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HEALING OF SIMPLE FRACTURES

AN EXPERIMENTAL STUDY *

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INTRODUCTION

This experimental study was undertaken to determine the changes occurring in the different tissues of long bones following simple fracture which finally result in osseous union of the fragments.

By simple fracture is meant one in which there has been solution of continuity of the cortical bone without separation of the fragments, or with reposition of the fragments to as nearly the normal position as possible and with a minimum of damage to the soft parts, especially to the periosteum.

The observations include: (1) the immediate changes in the bone and the surrounding soft parts following fracture that resulted from trauma, and (2) the changes constituting the inflammatory reaction which result in the repair of the fracture.

A description of the gross specimens was noted, roentgenographic examination made and, finally, the specimens were studied microscopically.

The different tissues involved in the process of repair, viz., the cortical bone, the periosteum and the marrow, were studied for the purpose of determining the precise rôle they played in the reparative process. These tissues vary somewhat in structure in the same animal at different ages and also in different bones of the different animals at the same age. These variations may be cited briefly.

PERIOSTEUM

In general the periosteum of young animals, children and adolescents is a strong white fibrous tissue membrane which is firmly united to the cortical bone in the region of the epiphyseal lines but elsewhere is more

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loosely attached by means of two kinds of fibers: (1) those derived from its fibrous layer which enter the bone (Sharpey's fibers), and (2) those in continuity with the organic basis of the bone (osteogenetic fibers) and which by branching are continuous with both the cellular and the fibrous layers. These delicate strands (columnellae) form arcades (described under marrow) on the surface of the bone, in the spaces of which are observed osteoblasts resting on the cortical surface, with osteal fibroblasts and fibroblasts occupying the meshes of the sustentacular tissue of the cellular layer, mainly in the order named from the cortex to the fibrous layer.

By differential staining with orcein it can be shown that the periosteum is well supplied with elastic fibrils, which run in various directions, for the most part parallel with the long axis of the bone.

The periosteum contains many blood vessels which subdivide rapidly before entering the cortical bone. As the blood vessels enter the haversian and Volkmann's canals, they are surrounded by delicate sheaths of areolar tissue. This will be termed reticulo-areolar (discussed under marrow) tissue within the haversian canals; through continuity with the endosteal arcades (discussed under marrow) it is attached to the wall of the canal and thus gives support to the more or less centrally located vessels. In the meshes of this tissue osteal fibroblasts are seen, especially in the meshes of the endosteal arcades.

The periosteum of the bones of young growing animals is therefore quite thick, vascular, elastic and abundantly supplied with osteoblasts in its deeper layer, as stated above.

If we compare this with the periosteum of an adult animal, one that has attained its growth, we find that the periosteum is relatively less thick, less vascular and elastic and that the osteoblasts are either flattened against the cortical surface as a single layer, visible at intervals or very difficult to recognize, or even absent.

CORTEX

Examination of the cortical bone also shows striking differences at different ages. The cortical bone of the young animal is thin; the haversian canals are relatively large and filled with a delicate reticulo-areolar tissue supporting the blood vessels, lymphatics and nerves. Lining the canals and in the meshes of the endosteal arcades are many osteoblasts. In the adult the cortical bone is relatively thick and dense; the haversian canals are small; osteoblasts are far less in evidence, and the endosteal arcades are flattened against the cortex.

Roentgenographic examination shows similar variations in thickness and density.

When the young bone is subjected to stress it often buckles, fissures and fragments. In some cases the lamellae seem to slide on each other and, as the result of mechanical bending, are compressed, crushing the interposed bone cells, without gross solution of continuity. Microscopically, small fissures are seen in the lamellae which do not extend through the entire thickness of the cortex, and areas of empty lacunae are seen.

When the bone of the adult is subjected to strain it frequently fractures in one plane like a cast iron rod.

MARROW

The marrow in the young is lymphoid in structure and quite vascular, while that of the adult is fatty and less vascular. Its sustentacular tissue is reticular tissue, which possesses a staining reaction to and the general appearance of the white fibers of areolar tissue proper. The latter consists of both white and elastic fibers, and its general name is connective tissue.

Areolar tissue accompanies the blood vessels that enter the bone, both by way of the nutrient foramina, Volkmann's canals and the subperiosteal terminations of the haversian canals, gradually becoming reduced in amount, according to the size and position of the vessels; about the smaller ramifications of the vessels it is found in minimal amount and passes insensibly into reticular sustentacular tissue.

The relative amount of areolar and reticular tissue in the marrow of the haversian canals and other diaphyseal spaces varies according to the size of the vessels. Therefore, it appears to the authors as more exact to speak of a reticulo-areolar tissue as supporting the vessels, nerves and marrow cells than to speak of it simply as areolar tissue. The latter can be both coarse and fine, but reticular tissue (white fibers alone) is a modified and fine form of areolar tissue.[1]

At the present time it is not intended to discuss the structure of the endosteum,[2] but simply to define our conception of the term "endosteal arcades." The marrow cavity, spaces and haversian canals are filled and lined by reticulo-areolar tissue, which supports the arterioles, numerous capillaries, lymphatics, nerves and marrow cells.

The lining tissue (endosteum) cannot be detached as a continuous membrane because it is reticular in structure: although only a part of the supporting tissue, in histologic sections it appears as a line of condensed tissue simulating a very delicate membrane. It is attached to the cortical walls by myriads of very slender threads. These fine threads are the columnellae, between and around which are continuous

1. Szymonowicz, in Schafer: Textbook of Microscopic Anatomy.
2. Also known as periosteum internum or membrana medullaris.

spaces (endosteal areolae) in which osteoclasts and osteoblasts can be observed resting against the cortical surfaces.

The columnellae form minute archways or "endosteal arcades." These arcades can readily be studied in sections of the femur of a human fetus at the sixth month of development. In adults the arcades are flattened against the cortical walls and are not clearly defined, except during constructive and rarefying activities.

For the foregoing reasons some writers hold that there is no such thing as an endosteum, because it cannot always be recognized apart from the general supporting structure with which it is continuous. Its position and function give it histologic and physiologic individuality.

FIBROBLASTS

It is essential that the reader should have a clear idea of what the authors understand by fibroblasts, osteoblasts and osteoclasts. A discussion regarding their origin and function is reserved for a future article.

The fibroblast, as its name implies, is a fiber producing cell of mesenchymal origin. It is the cell of embryonic connective tissue, a cell that possesses wonderful inherent potentialities; this becomes manifest as it is studied in the development and the repair of tissue.

Fibroblasts vary in shape in different situations. Usually they are flat elongate cells with long processes, and have flat oval and clear nuclei that lie more or less centrally; young forms without processes may resemble, and in fact have been classed with, epithelioid cells. They differentiate according to histogenetic demands. Fibroblasts can be well studied in granulation tissue, in the cellular layer of the periosteum, and in the developing fibrous callus or fibrous marrow of healing fractures.

The proliferating cells of embryonic connective tissue are always larger than the cells of fully developed resting connective tissue, which are relatively poor in protoplasm. Since these proliferating cells are the antecedents of the future tissues, they are known as formative cells. Those giving rise to fibrous connective tissue are called fibroblasts, while those forming cartilage are termed chondral fibroblasts (chondroblasts), and those forming bone become osteal fibroblasts (osteoblasts).

OSTEOBLASTS

Osteoblasts are usually recognized as forming a line on the surface of bone and varying greatly in form according to the degree and character of functional activitiy. They may also be recognized when occurring in other situations. In form they are relatively large; they may be flattened, round, oval, low cylindrical or cubical, subfusiform with eccentric nucleus or with processes. They are rich in protoplasm and the processes indicate motility.

OSTEOCLASTS

Osteoclasts are polymorphic multinucleate giant cells without a definite limiting membrane, and are recognized by being in contact with or near to the surface of bone.

When in contact with bone they usually occupy depressions, varying in depth, which they produce by erosion.

It is believed that fibroblasts and osteoblasts have a common origin, either from the formative cells of embryonic connective tissue or by the differentiation of the early fibroblast under direct histogenetic demand. Much doubt exists among writers as to the real origin of the osteoclasts.

TECHNIC

The animals used were kittens. Under ether anesthesia the right humerus was fractured by bending across the ends of the thumbs.

Fracture occurred with or without an audible snap. On recovery from the anesthetic the animal walked about on the fractured leg; no attempt at immobilization was made.

The animals were killed with chloroform at intervals of from twelve hours to thirty-four days, with the exception of Kitten 1, which died three and one-half days after fracture, apparently from suffocation by cuddling of its companions.

Eighteen fractures were produced. The right humerus was used in all cases.

All fractures in which sufficient time was given healed by osseous union, but ossification did not progress at the same rate of speed in all cases, as shown by the microscopic study of sections.

When microscopic examination of two specimens differing by several days' duration of experiment showed approximately the same histologic picture, we have omitted the description of one of these.

PROTOCOLS

EXPERIMENT 1.—Kitten 7, a small, poorly nourished female, was used; the duration of the experiment was twelve hours.

Gross Examination.—The humerus was straight and apparently firm. Palpation revealed some flattening of the shaft but no inflammatory thickening. There was no mobility on gentle manipulation.

Roentgenographic Examination.—There was a slight irregularity of the cortex on the lateral surface of the shaft, with longitudinal fissuring of the cortical bone.

Microscopic Examination.—The cortical bone was moderately thick; the haversian canals were large and numerous. On the lateral aspect of the shaft near its middle, there was an interruption of the cortical bone with slight fragmentation; on the opposite side the cortex was continuous throughout but had been bent inward toward the marrow.

The periosteum was intact throughout and was adherent to the bone except at the line of fracture, where it was stripped up for a short distance. There

was no subperiosteal hemorrhage. The periosteal cells (osteal fibroblasts) were not abundant, but were most evident in the areas where the haversian canals open onto the surface of the cortical bone. In the immediate vicinity of the fracture line some of the lacunae were vacant, but beyond this area groups of vacant lacunae were seen scattered about with intervening areas in which the bone cells were well stained. On the side opposite the fracture line, numerous well stained bone cells were seen. The haversian canals were large but showed nothing remarkable. The marrow was lymphoid, congested and edematous with scattered areas of hemorrhage in the immediate vicinity of the fracture line.

Fig. 1 (Kitten 7).—Gross section of diaphysis of humerus; the duration of the experiment was twelve hours.

In the medullary portion of the bone on a level with the fracture line, there were several large, irregular clear spaces apparently filled with serous exudate in the recent state. There was no evidence of fibroblastic, osteoblastic or osteoclastic activity. The muscles about the line of fracture were edematous and there was a small amount of leukocytic infiltration.

EXPERIMENT 2.—Kitten 1, a small and poorly nourished male, was used; the duration of the experiment was three and one-half days.

Gross Examination.—Fragments were angulated at the line of fracture, and movable with a slight force.

Roentgenographic Examination.—There was a transverse fracture of the shaft of the humerus a little below its middle. Fragments were angulated about 75 degrees internally. The medial side of the proximal end of the distal fragment lay across the distal end of the proximal fragment. There was no evidence of callus formation.

Microscopic Examination.—There was complete fracture of the shaft of the humerus with a large amount of hemorrhage into the medullary portion of the fragments, beneath the periosteum and external to the latter especially on the side of angulation.

The cortical bone was relatively thin, and the haversian canals were relatively large and numerous. There had been longitudinal fissuring as well as fragmentation with some stripping up and curling, so that at the line of fracture the cortex was irregular. Bone cells were absent from the lacunae for some distance from the fracture line. In one place an haversian canal was seen running obliquely through the cortex, opening on one hand beneath the periosteum and on the other into the marrow cavity; at the latter opening very few cells were seen, while in the canal cells that formed a continuous line with those beneath the periosteum were seen.

The periosteum was quite thick and there were several layers of osteoblasts in the looser fibro-elastic tissue next to the cortical bone. It was continuous on the side of angulation, but had been stretched and hence thinned out and stripped off the cortical bone for some distance on either side of the fracture

Fig. 2 (Kitten 7).—Humerus, showing longitudinal fissure at middle of diaphysis; the duration of the experiment was twelve hours.

line, and was relaxed and wavy. In one place cleavage had occurred between the dense fibrous and the loose fibro-elastic layers; the latter with its several layers of osteoblasts was adherent to the bone. Between the raised up periosteum and the cortical bone there was coagulated blood with small fragments of bone.

On the side opposite the angulation the periosteum had been lacerated flush with the fracture line, and had retracted for a short distance, leaving the cortical bone of each fragment denuded and in contact with the surrounding fibrous tissue and muscles, which had been drawn tightly against the ends of the fragments and across the interval of separation. Where the periosteum was present it was closely attached to the underlying cortical bone; here, the osteoblasts were evident as several layers.

In the immediate vicinity of the fracture line on each side, the periosteum was thickened for a considerable distance by serous and cellular infiltration.

The medullary portion of the bone in the vicinity of the fracture line was filled with blood clot, which was continuous with that beneath the lifted up

periosteum on the side of angulation. Beyond the blood clot in each fragment the marrow was lymphoid and its capillary blood vessels were widely dilated and engorged with blood. The congestion of these vessels was conspicuous under the microscope, the marrow was edematous and there was a moderate amount of leukocytic infiltration, with many polymorphonuclear leukocytes. At the margin of the clot in the marrow there was a beginning organization as could be seen by the proliferation of fibroblasts, with beginning invasion of the clot. Along the inner surface of the cortical bone, there was an evident

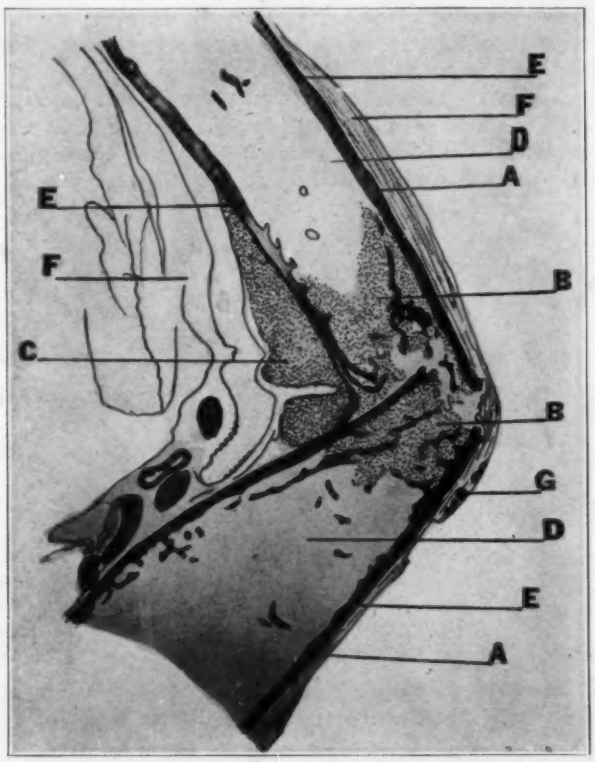

Fig. 3 (Kitten 1).—Camera lucida drawing of longitudinal section at site of fracture of humerus; the duration of the experiment was three and one-half days. *A*, periosteum (continuity on side of angulation and rupture on opposite side); *B*, area of hemorrhage within medullary cavity; *C*, area of hemorrhage external to periosteum; *D*, region of edematous and congested marrow; *E*, relatively thin elastic cortex (incurving at line of fracture in one place); *F*, muscles and fascial sheaths, and *G*, radial nerve.

increase in the endothelial leukocytes; while osteoblasts might be present none could be positively recognized nor were there any along the osseous surface.

EXPERIMENT 3.—Kitten 6, a poorly nourished male, was used; the duration of the experiment was five days.

Gross Examination.—There was no evident change in form; slight mobility was present on bending.

Roentgenographic Examination.—There was a buckling fracture of the mid-portion of the shaft of the humerus with slight internal angulation. On the side of angulation the cortex was buckled, and several small spots of increased density in the immediate vicinity of the fracture line were probably fragments of cortical bone. One of these extended inward from the upper end of the lower fragment. The cortical bone on the side opposite the angulation appeared to be continuous; there was no evidence of callus formation.

Microscopic Examination.—There was a complete fracture with buckling and internal angulation.

The cortical bone was relatively dense; the haversian canals were relatively small but numerous. There had been fissuring and fragmentation of the end of the major fragments. These small fragments as well as the cortical bone for varying distances on either side of the fracture line showed numerous empty lacunae, while beyond this the bone cells stained well and regularly. The haversian canals varied considerably in size and were for the most part quite free from blood clot. The periosteum was intact except in a small area at the level of the fracture line. Here it had been stretched and thinned out,

Fig. 4 (Kitten 1).—Fracture of humerus; the duration of the experiment was three and one-half days.

and some of its fibers had been lacerated. Clear spaces were seen between the periosteum and the cortical bone. The line of cleavage extended through the cellular layer of the periosteum, so that osteal fibroblasts adhered to both the periosteum and the bone. In some areas the osteal fibroblasts were absent, apparently having been washed away during preparation. On the side of angulation there was an area of hemorrhage for the most part external to the periosteum, which was being invaded by leukocytes. Along the outer surface of the cortex and the inner surface of the periosteum there was evidence of fibroblastic proliferation, but there was no evidence of callus formation.

In the region of the fracture line there had been considerable hemorrhage into the medullary portion of the bone. The blood clot had been replaced largely by a cellular, vascular and edematous fibrous marrow, the procallus granulation tissue. In the fibrous marrow, especially about some of the trabeculae and along the cortical bone, there were areas of beginning osteoblastic proliferation. Proximal and distal to the fibrous marrow, the marrow was lymphoid in structure and at the junction of the two types of marrow the

vessels were dilated and engorged with blood. At the line of fracture, there was an open fissure or cleft occupied by serous exudate. The walls of this cleft showed fragments of blood clot. The surrounding muscles at the region of fracture showed a small amount of leukocytic infiltration.

EXPERIMENT 4.—Kitten 11, a poorly nourished female, was used; the duration of the experiment was ten days.

Gross Examination.—There was a distinct external bowing with an evident rounded callus at the site of fracture. A slight movement could be produced by bending in different directions.

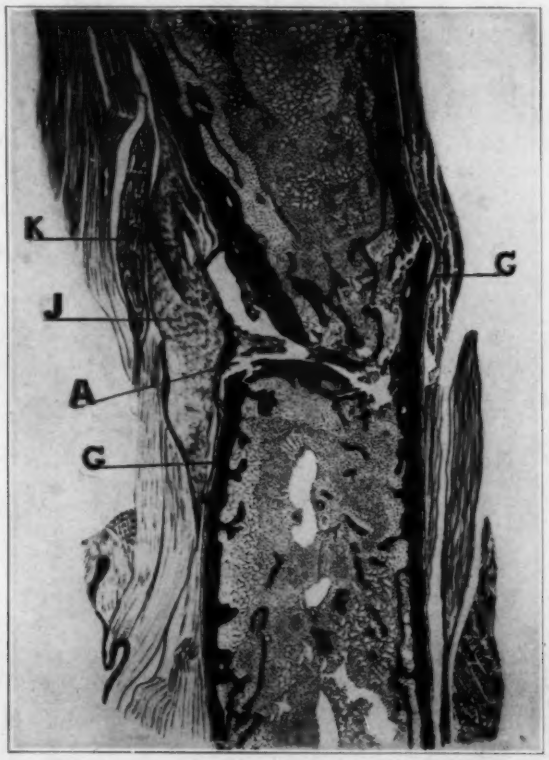

Fig. 5 (Kitten 6).—Camera lucida drawing of longitudinal section at site of fracture of humerus; the duration of the experiment was five days. *A*, line of fracture; *J*, area of hemorrhage external to periosteum; *G*, periosteum, and *K*, radial nerve.

Roentgenographic Examination.—There was complete fracture of the midportion of the humerus with slight impaction and internal angulation of about 35 degrees. There was no evidence of osseous callus about the ends of the fragments.

Microscopic Examination.—There was a complete fracture with internal angulation, slight overriding and lateral displacement of the proximal fragment. The cortical bone was relatively thin, and the haversian canals were relatively large. There had been fragmentation of the ends of the bone. For a considerable distance on either side of the fracture line the lacunae were vacant; farther away bone cells gradually and irregularly made their appear-

ance in the lacunae. The haversian canals were becoming irregularly enlarged by ingrowth of delicate vascular tufts. In some of these canals one saw well defined osteoclasts. There was little if any evidence of new bone formation within the haversian canals, but there was distinct evidence of beginning new bone formation on the inner and outer surface of the dead cortex as well as on the surface of the trabeculae. Between the major fragments there was a considerable amount of hemorrhagic débris and an empty space marked the line of fracture.

The periosteum was of moderate thickness and had been lifted up from the cortical bone for a considerable distance on either side of the fracture line. On the side of angulation there had been laceration of the periosteum. In the area of laceration a wedge of dense fibrous tissue extended inward toward the cortical bone and separated the cartilaginous callus. On the side opposite the angulation the periosteum was continuous, and the subperiosteal cartilaginous callus was continuous from fragment to fragment.

Fig. 6 (Kitten 6).—Fracture of humerus; the duration of the experiment was five days.

The subperiosteal callus was abundant and mostly cartilaginous in character. On either side of the fracture line, in the angle between the periosteum and the cortical bone, this had undergone ossification and the newly formed trabeculae, which were osteoid in character, extended for the most part at right angles to the cortical bone. The older portions of the osseous subperiosteal callus were next the cortical bone, while beneath the periosteum the callus was still cartilaginous but was undergoing ossification. The surfaces of the new-formed trabeculae were covered with osteoblasts. The central and widest portion of the subperiosteal callus was still cartilaginous save on the side of angulation, where the wedge of fibrous tissue mentioned in the foregoing extended inward and separated it into two parts.

The medullary canal in the region of the fracture was filled with fibrous callus, rich in capillaries. About the empty space between the major fragments there were bone fragments surrounded by débris. The lacunae of the bone fragments were empty. In some the surfaces were very irregular, sur-

rounded by fibrous callus, and Howship's lacunae with osteoclasts were seen; other fragments showed no evidence of absorption. Along the inner side of the cortical bone as well as the adjacent trabeculae, new bone was being deposited; new trabeculae also were being formed by ossification of the fibrous callus without an intervening cartilaginous stage. Beyond the fibrous callus, the marrow was fibrous and edematous, and still further away the marrow became lymphoid in character. Osteoclasts were abundant on the surfaces of the trabeculae both old and new.

EXPERIMENT 5.—Kitten 3, a moderately well nourished female, was used; the duration of the experiment was twelve days.

Gross Examination.—There was slight angulation, and a distinct oval callus was present, with a slight movement between the fragments on careful bending. The union apparently was fibrocartilaginous.

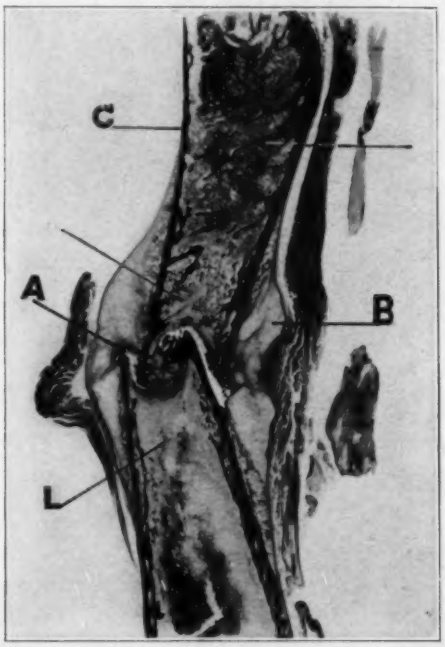

Fig 7 (Kitten 11).—Longitudinal section at site of fracture of humerus; the duration of the experiment was ten days. *A*, line of fracture; *B*, subperiosteal callus, largely cartilaginous, osteoid in the angles between the periosteum and the cortex; *C*, cortex; thinness should be noted; *D*, medullary callus, fibrous and osteoid; *E*, lymphoid marrow, and *L*, region of edematous marrow.

Roentgenographic Examination.—There was a fracture of the midportion of the shaft of the humerus with slight internal angulation and lateral displacement of the upper end of the lower fragment. There was an increase in density of the medullary portion of the fragments at the fracture line—probably ossified internal callus and some periosteal callus on each fragment near the fracture line, which did not extend across the fracture line. Apparently there was no osseous union.

Microscopic Examination.—This showed complete fracture with slight lateral displacement of the distal fragment and overriding.

The cortical bone was fairly thick, and the haversian canals for the most part were small. The cortex of the proxical fragment on the mesial side was bent inward toward the marrow, partially blocking the medullary portion. There also was fragmentation of the ends of the cortical bone at the fracture line. Blood clot was absent except a small amount between the ends of the major fragments. The radial nerve was seen on the surface of the callus.

The periosteum had been stripped up all around in an area corresponding to the middle third of the shaft; there also had been laceration of the periosteum at the level of the fracture line. There was considerable subperiosteal callus. This was osteoid in the angle between the periosteum and the cortical bone, both proximal and distal to the fracture line, the older portion being next the cortical bone. Its marrow spaces were filled with loose fibrous marrow with blood vessels and a few marrow cells. Opposite the fracture line the callus was cartilaginous, most abundant on the side of angulation, but encircling the ends of the fragments. The older portions of the callus were next to the cortical bone. The trabeculae of the subperiosteal osteoid callus were irregular and were fused to the cortical bone by a layer of new-

Fig. 8 (Kitten 11).—Fracture of humerus; the duration of the experiment was ten days.

formed bone, which united the trabeculae, while toward the periosteum the trabeculae were in a later stage of development. The surfaces of the latter were serrated, and the projecting trabeculae were not united by a layer of new-formed bone beneath the periosteum. Many osteoblasts were also seen.

EXPERIMENT 6.—Kitten, a fairly well nourished female, was used; the duration of the experiment was fourteen days.

Gross Examination.—There was no noticeable angulation; a smooth oval callus was palpable; no mobility of the fragments was seen.

Roentgenographic Examination.—There was a buckling fracture of the middle of the shaft of the humerus, with internal angulation of about 10 degrees and a slight overriding of the cortical bone on the side of angulation. The fragments were united by bony union and there was nearly a millimeter of subperiosteal new bone laid down. On the side of angulation at the fracture line there was a small spot of decreased density which was interpreted as cartilaginous callus; on the side opposite the angulation the subperiosteal callus was of equal density throughout. There was a well defined medullary

osseous callus extending across the bone at the line of fracture and along the inner surface of the cortex of each fragment.

Microscopic Examination.—A complete fracture was present. The fragments overrode on the side of angulation, and the cortical bone had been fractured in two places, producing a wedge shaped fragment which lay between and in line with the major fragments. A thin strip of bone from the internal surface of the cortex was continuous from one major fragment to the other, and because of the overriding this strip had been bent into the medullary portion of the bone.

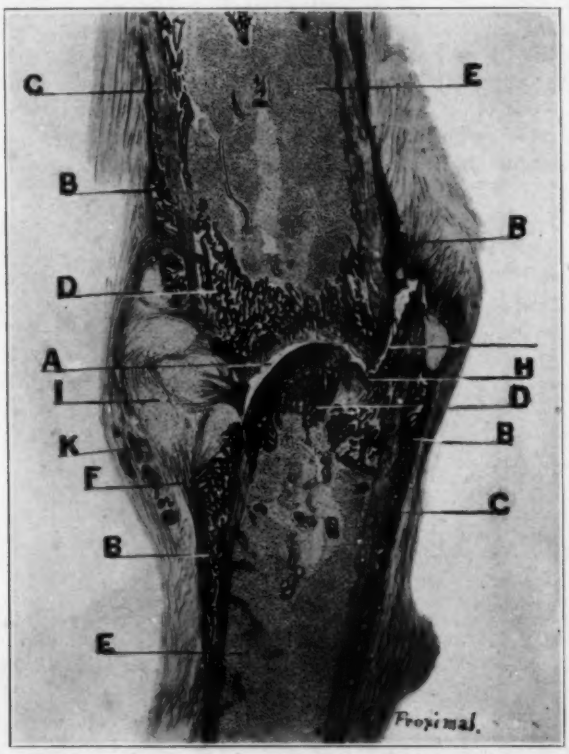

Fig. 9 (Kitten 3).—Camera lucida drawing of longitudinal section at site of fracture of humerus; the duration of the experiment was twelve days. *A*, line of fracture; *B*, subperiosteal osseous callus; *C*, cortex; *D*, medullary osseous callus; *E*, lymphoid marrow; *F*, interrupted periosteum; *H*, fragment on borderline of fibrous marrow and line of fracture; *I*, cartilaginous callus undergoing fibroblastic invasion, and *K*, divisions of radial nerve. The section is inverted.

The cortical bone was moderately thick and the haversian canals were small. There had been considerable fragmentation at the line of fracture. The cortical bone of each fragment for a short distance on either side of the fracture line showed vacant lacunae; the surface was irregular and vascular tufts from the subperiosteal and medullary sides were pushing their way into irregular spaces; a few osteoblasts were seen.

The periosteum was thick and its inner layer quite cellular; osteoblasts were present in moderate numbers. It had been lifted up from the cortical bone

on either side of the fracture for fully two-thirds the length of the diaphysis and had been lacerated on the side of angulation. There was a well developed subperiosteal osseous callus surrounding and uniting the fragments, except on the side of angulation, where the periosteum had been lacerated. Here the callus was still cartilaginous but it was undergoing ossification.

The subperiosteal osseous callus was firmly united to the cortical bone and a sharp line of demarcation was clearly seen between the two. On the side of angulation where there had been a laceration of the periosteum, the subperiosteal callus was interrupted at the line of fracture by fibrous tissue in which there was an island of ossification and some fibrocartilage. The small amount of cartilaginous callus opposite the fracture line was undergoing ossification. On the side opposite the angulation, where the periosteum had remained intact, the subperiosteal callus was continuous from one fragment to the other. The subperiosteal callus tapered off on either side of the fracture line to an equal extent—almost to the epiphyseal line. While irregular, the

Fig. 10 (Kitten 3).—Fracture of humerus; the duration of the experiment was twelve days.

trabeculae were arranged largely parallel to, others at right angles to, the cortical bone. The bone cells stained well and there were many osteoblasts on the surface of the trabeculae.

The marrow was fibrous and quite vascular. There was a well defined osseous medullary callus extending across the medullary portion of the bone with the maximum thickness at the fracture line; this extended along the inner surface of the cortical cylinder for some distance, gradually tapering off. There was no intermediate callus and remains of blood clot were seen between the cortical ends of the fragments. The marrow of the subperiosteal and medullary calluses was fibrous and delicate. In some areas lymphoid marrow was making its appearance. Beyond the medullary callus the marrow was lymphoid.

EXPERIMENT 7.—Kitten 8, a small and fairly well nourished female, was used; the duration of the experiment was twenty days.

Gross Examination.—There was slight deformity, and palpation revealed a distinct rounded callus. No mobility was seen on attempted bending.

Roentgenographic Examination.—There was a complete fracture of the middle of the shaft of the humerus with a slight internal angulation and slight lateral displacement of the lower end of the upper fragment with overriding. There was considerable subperiosteal osseous callus which was less dense and easily differentiated from the cortical bone. On the lateral surface of the shaft at the level of the fracture line, there was a large rounded callus, less dense than that above and below, which was probably cartilaginous in structure.

Microscopic Examination.—This showed a complete fracture with lateral displacement and overriding of the proximal fragment and slight internal angulation.

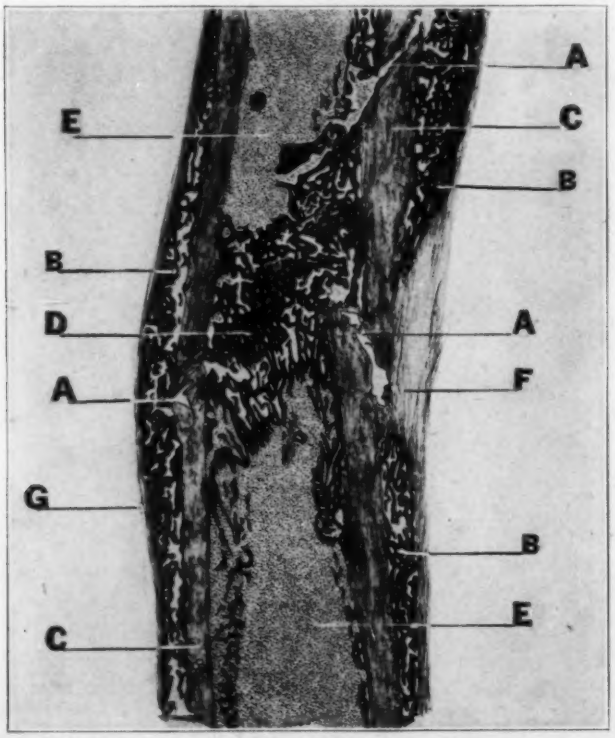

Fig. 11 (Kitten 2).—Camera lucida drawing of longitudinal section at site of fracture of humerus; the duration of the experiment was fourteen days. *A*, line of fracture; *B*, subperiosteal osseous callus; *C*, old cortex; *D*, medullary osseous callus (extending along the inner surface of the cortex); *F*, periosteum interrupted, and *G*, periosteum.

The cortical bone was thick, and the haversian canals were relatively numerous and large. There had been slight fragmentation. In the immediate vicinity of the fracture line the lacunae were empty; farther away, however, the bone cells appeared in irregular areas with intervening areas of empty lacunae. Still farther the lacunae were occupied by well stained bone cells.

The haversian canals in the areas in which the lacunae were empty were occupied by a delicate reticular tissue supporting blood vessels filled with blood. The walls of the canals were lined with osteoblasts, and new bone was being deposited which was clearly differentiated from the surrounding dead bone. Farther away from the line of fracture the haversian canals were filled with lymphoid marrow.

After twenty days it was difficult to determine whether or not there had been a complete laceration of the periosteum. On one side the periosteum was thinned out but continuous over the large subperiosteal callus. As it varied considerably in thickness and arrangement of its fibers, there had probably been a laceration which had healed. On the opposite side the periosteum extended into and was lost in the cartilaginous callus, and the periosteum of the two fragments lay at different levels. As the central portion of this subperiosteal callus lay in contact with muscle, while that above and below was covered with periosteum, there had undoubtedly been a laceration of the periosteum here.

Fig. 12 (Kitten 2).—Fracture of humerus; the duration of the experiment was fourteen days.

The subperiosteal callus was partly osseous and partly cartilaginous. The osseous callus was present in the angle between the raised periosteum and the cortical bone and seemed to have sprung from the cortex. Between the osseous subperiosteal calluses there was cartilaginous callus which was being invaded by vascular tufts from the osseous callus and was being replaced by osteoid callus. The fibrous marrow was present in these spaces where ossification was progressing; elsewhere, in the older spaces, it was becoming lymphoid. A sharp line of demarcation was seen between the new bone and the original cortical bone. Blood vessels were seen in the marrow spaces of the developing osseous callus. The tips of many of the trabeculae of the osseous callus in contact with the periosteum were capped by osteoclasts. These cells also were seen here and there in the marrow spaces, usually on the trabeculae. They stained deeply.

In the medullary portion of the bone at the level of the fracture line the callus consisted of moderately dense, very cellular and vascular fibrous tissue. In one of the fragments the entire medullary canal at the fracture line was closed by an osseous callus, the trabeculae of which extended for the most part parallel to the long axis of the fragment. The bone cells of the trabeculae stained well, and their surfaces were covered by several layers of osteoblasts. The marrow spaces contained fibrous marrow supporting blood capillaries. This fibrous marrow passed into the osseous stage without an intermediary cartilaginous stage. The marrow throughout the medullary canal beyond the fracture area was dense and lymphoid in character, with a small number of fat cells. Near the medullary callus it changed quite abruptly into

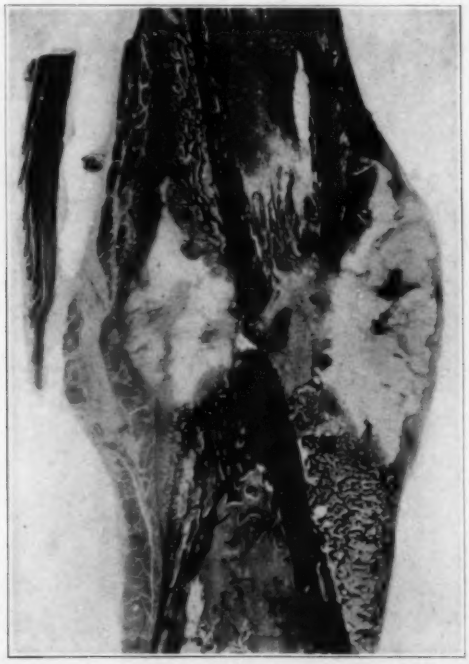

Fig 13 (Kitten 8).—Longitudinal section at site of fracture of humerus; the duration of the experiment was twenty days. There is angular displacement; the plane of sectioning is not sagittal to the angulation. The large amount of subperiosteal callus, largely cartilaginous opposite the line of fracture, should be noted; this is osteoid in the angles between the cortex and the periosteum.

edematous fibrous marrow. The medullary callus was firmly united to the cortical bone and a sharp line of demarcation was seen between the two.

In the fibrous callus between the major fragments and in the line of fracture, there were small fragments with Howship's lacunae, in which osteoclasts varying in size were seen. The ends of the major fragments were in part irregular from osteoclastic action, and osteoclasts were abundant here. In places a thin layer of new bone was present, making the surface even. Where the bone ends were covered with hemorrhagic débris no such changes had taken place.

EXPERIMENT 8.—Kitten 15, a fairly well nourished female, was used; the duration of the experiment was twenty-eight days.

Gross Examination.—There was a slight bowing with a small amount of thickening due to callus. No mobility was noted, the union apparently being solid.

Roentgenographic Examination.—There had been a fracture of the shaft of the humerus a little below the middle, with slight internal angulation. On the side of the angulation the periosteum had been lifted off the cortical bone for a considerable distance, and the subperiosteal osseous callus had completely bridged across the line of fracture. The original cortical bone was still visible and there had been a slight buckling on the side of the angulation. On the side opposite the angulation the cortical bone was continuous but thickened, probably by the deposition of the subperiosteal osseous callus. There was an area of increased density in the medullary portion at the site of the fracture. The internal or medullary osseous callus was seen uniting the fragments.

Fig. 14 (Kitten 8).—Fracture of humerus; the duration of the experiment was twenty days.

Microscopic Examination.—There had been a buckling fracture of the shaft of the humerus with internal angulation and lifting up of the periosteum, most marked on the side of the angulation.

The cortical bone was relatively thick and dense, and the haversian canals for the most part were small. In several areas these canals had been irregularly enlarged by osteoclastic action and were filled with reticular tissue supporting blood vessels. Their walls were lined in places by osteoclasts and in these places osteoblasts were absent or few in number; there was no evidence of new bone formation. In other parts of the same spaces osteoblasts were numerous and new bone was being deposited. A sharp line of demarcation was seen between the old and the new bone; this was most marked on the side of the angulation. On the side opposite the angulation the outer portion of the cortical bone had remained intact, but the inner portion had buckled and

fragmented. In the area of fracture the dead cortical bone was becoming rarefied. Large irregular spaces filled with fibrous marrow supporting blood vessels and lined with numerous osteoclasts were seen. The cortex showed vacant lacunae.

The periosteum was thick, the deep layer quite cellular. It had been lacerated on the side of angulation but was intact on the opposite side.

The subperiosteal callus was most marked on the side of angulation. The greater part of this had undergone ossification. The older osseous portions of the callus were away from the line of fracture, while in the immediate

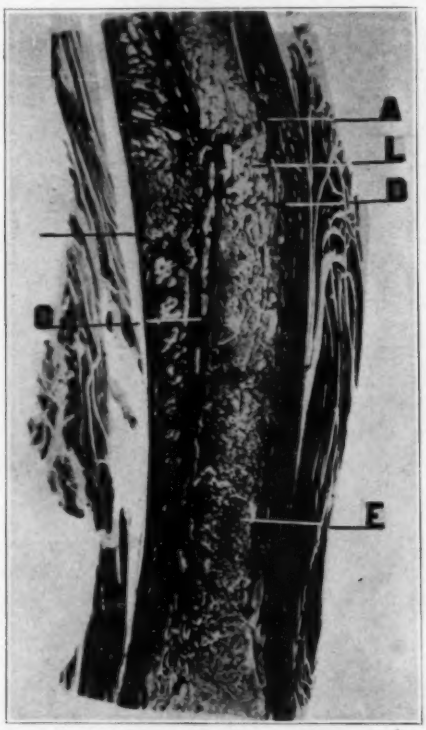

Fig. 15 (Kitten 15).—Longitudinal section of site of fracture of humerus; the duration of the experiment was twenty-eight days. *A*, line of fracture; *B*, abundant subperiosteal osseous callus (straightening of diaphysis); *C*, cortex (rarefaction); *D*, medullary osseous callus; *E*, lymphoid marrow, and *L*, region of fibrous marrow (fibrous callus).

vicinity of the fracture line, under the area of periosteal laceration, the callus was still in part cartilaginous and in part osteoid in character; this, however, was undergoing ossification. Numerous osteoblasts were present on the surface of the new trabeculae, and in some areas osteoclasts were present in large numbers. In other areas, especially on the surface of the dead bone, the osteoblasts were few in number or absent. Here many osteoclasts were seen. The marrow spaces were filled with fine reticulo-areolar tissue supporting blood vessels.

In the medullary portion of the bone in the area of fracture, a medullary or internal callus had developed which extended across the line of fracture for

a varying distance into each fragment; this was firmly united to the inner surface of the cortical bone; a sharp line of demarcation between the ossified callus and the old cortex was visible. The osseous trabeculae of the callus were in part covered by a line of closely placed osteoblasts; in considerable areas, however, osteoblasts were absent and were replaced by numerous osteoclasts. Here the surface of the trabeculae was very irregular. The marrow spaces were filled with lymphoid and a considerable amount of fatty marrow.

EXPERIMENT 9.—Kitten 4, a well nourished, older cat, was used; the duration of the experiment was thirty days.

Gross Examination.—There were no deformity, no thickening at the site of the fracture, and no mobility of the fragments.

Fig. 16 (Kitten 15).—Fracture of humerus; the duration of the experiment was twenty-eight days.

Roentgenographic Examination.—There was a buckling fracture at the midportion of the shaft of the humerus with slight internal angulation. On the side of the angulation the cortical bone had buckled; the periosteum had been lifted up, and there was an area of increased density bridging the line of fracture, which was osseous subperiosteal callus. This restored the normal thickness of the shaft in this region. The cortical bone opposite the side of angulation had been bent slightly and showed some irregular increase in thickness. There was no increase in density of the medullary portion at the fracture line.

Microscopic Examination.—There was slight buckling with internal angulation. The cortical bone was relatively thick and the haversian canals were large. On the side of angulation there had been a buckling of the cortical bone and longitudinal fissuring. On the side opposite the angulation the cortical bone had undergone bending with the longitudinal shifting of the lamellae and fracture of some of these.

The cortical bone in the immediate vicinity of the fracture line showed empty lacunae. The haversian canals were large and the fibrous marrow was pushing its way into the old cortical bone, which was being absorbed. Absorption was manifest by large haversian spaces, by a thinning out of the bone and by its marked irregularity—fragmentation. The surrounding and adjacent connective tissue and the muscles showed but little cellular infiltration. Slight edema was present.

The periosteum had remained intact, but had been lifted up on the side of angulation for some distance on either side of the fracture line. Between the lifted up periosteum and the buckled cortical bone there was a large sub-

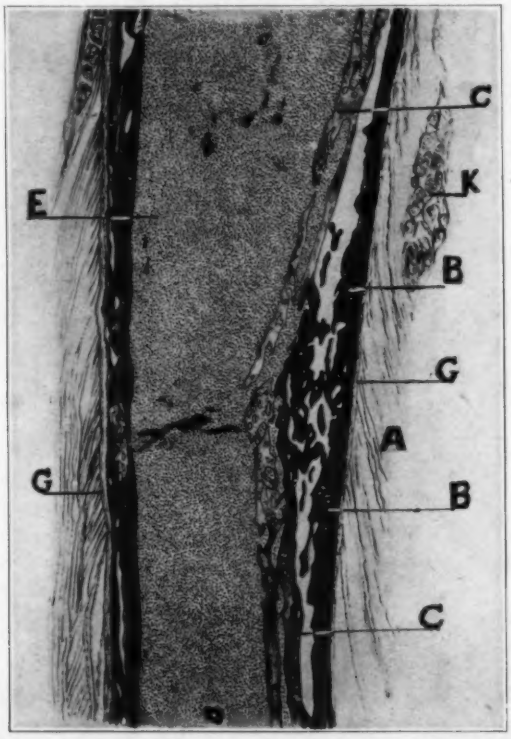

Fig. 17 (Kitten 4).—Camera lucida drawing of longitudinal section at site of fracture of humerus; the duration of the experiment was thirty days. *A*, buckling fracture; *B*, subperiosteal callus and new cortex (straightening of diaphysis); *C*, old cortex (rarefaction); *E*, lymphoid marrow; *G*, periosteum in continuity; *K*, radial nerve.

periosteal osseous callus, which was continuous across the line of fracture and of greatest thickness at this line. The marrow was fibrous, but lymphoid marrow cells were beginning to appear. On the side opposite the angulation the periosteum had been detached from the cortical bone but had not been lifted up to any extent. A small layer of new bone had been deposited and the line of union between this and the original cortical bone was wavy and irregular but sharply defined. In some of the sections, at the level of the fracture line remnants of a medullary osseous callus were seen extending across the medullary portion of the bone and along the inner surface of the original cortex;

that these trabeculae were not fragments of cortical bone was shown by the large size of the cells, their irregular position, their staining quality and the presence of osteoid material. The marrow was lymphoid.

EXPERIMENT 10.—Kitten 14, a well nourished female, was used; the duration of the experiment was thirty-two days.

Gross Examination.—About 35 degrees of internal angulation was present; there was a large rounded callus, but no mobility was noted between the fragments on attempted bending or twisting.

Roentgenographic Examination.—There had been a complete fracture of the shaft of the humerus at about its middle portion with internal angulation. The periosteum had been lifted up and considerable subperiosteal callus had been deposited. Most of this callus was osseous but at the level of the fracture line the area of decreased density indicated that at this point the callus had

Fig. 18 (Kitten 4).—Fracture of humerus; the duration of the experiment was thirty days.

not as yet become osseous. The medullary portion of the fragments in the vicinity of the fracture line showed increased density which was interpreted as osseous medullary callus.

Microscopic Examination.—There had been a complete fracture, with internal angulation and slight lateral displacement of the lower end of the upper fragment, so that the medial portion of the cortical bone of the proximal fragment was embedded in the medullary portion of the upper end of the distal fragment. There was no fragmentation.

The cortical bone was relatively thick and dense and the haversian canals were relatively small; on either side of the fracture line the lacunae were vacant for a considerable distance; here the haversian canals had undergone marked enlargement so that there was considerable rarefaction of the original cortex. Farther away from the fracture the bone cells gradu-

ally and irregularly made their appearance. There was no noticeable fragmentation. The smaller haversian canals contained blood vessels surrounded by a small amount of reticulo-areolar tissue. In the larger canals the surrounding bone was undergoing rarefaction. In these we saw blood vessels supported by a large amount of fibrous marrow and lymphoid marrow. These larger haversian canals or marrow spaces were irregular in outline and were lined by osteoblasts and osteoclasts, and new bone was being deposited on the surface of old bone.

The periosteum was of moderate thickness and had been lacerated and lifted off the cortical bone. The laceration was most marked on the side of the

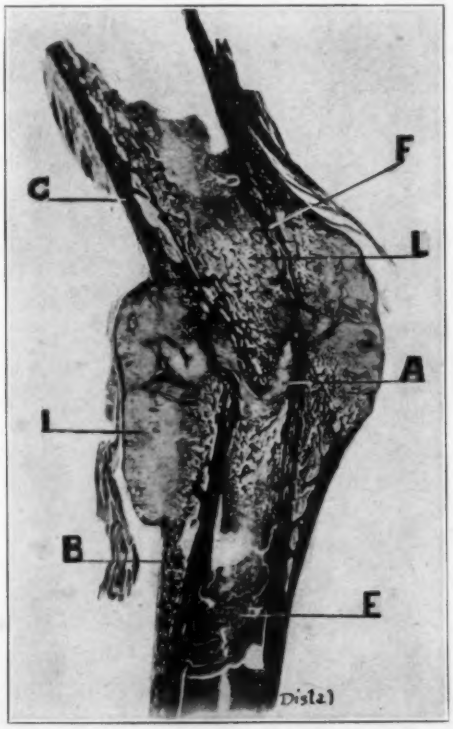

Fig. 19 (Kitten 14).—Longitudinal section at site of fracture of humerus; the duration of the experiment was thirty-two days. *A*, line of fracture (medullary cartilaginous callus between the osseous calluses); *B*, subperiosteal osseous callus; *C*, cortex; *E*, lymphoid marrow; *I*, large subperiosteal cartilaginous callus; *F*, rarefied cortex, and *L*, region of fibrous and edematous marrow.

angulation. Between the lifted up periosteum and the cortical bone there was a large amount of subperiosteal callus, in various stages of ossification, the oldest portions being nearest the cortical bone. In the angle between the periosteum and the cortical bone the callus had undergone ossification. Here well defined trabeculae and marrow spaces filled with lymphoid marrow were seen. The older portions of the osseous callus were next to and firmly united to the cortical bone. Osseous callus was less abundant on the side of angulation. Between the osseous calluses, especially at the level of the fracture line, there was fibrous and fibrocartilaginous callus which was undergoing

ossification by ingrowth of vessels from the osseous callus. Several small apparently independent centers of ossification were seen in the fibrocartilaginous callus. The ends of the lacterated periosteum were embedded in the fibrocartilaginous callus and the subperiosteal callus was covered by new periosteum.

The medullary portion of the fragments at the site of fracture was occupied by a fibrous and fibrocartilaginous callus, which was continuous with the subperiosteal callus between the ends of the fragments. This was undergoing ossification from the inner side of the cortical bone so that bone trabeculae extended across the medullary portion of each fragment. At the line of fracture the fragments were united by cartilaginous callus. A sharp line of demarcation was visible between the ossifying medullary callus and the dead cortical bone. The marrow spaces of the medullary osseous callus were filled

Fig. 20 (Kitten 14).—Fracture of humerus; the duration of the experiment was thirty-two days.

with fibrous marrow and a moderate amount of lymphoid marrow. The new bone trabeculae were surrounded by numerous osteoblasts, and a moderate number of osteoclasts were seen on the surface of the trabeculae, especially about the roughened ends of the cortical fragments, frequently not resting in Howship's lacunae. Proximal and distal to the medullary callus the marrow was lymphoid with small amounts of fat.

EXPERIMENT 11.—Kitten 16, a well nourished male, was used; the duration of the experiment was thirty-four days.

Gross Examination.—No deformity was present, but there was a large rounded callus. There was no mobility of the fragments, the union being solid.

Microscopic Examination.—There had been a complete transverse fracture at about the midportion of the shaft of the humerus, with lateral displacement to the extent of about one-half the diameter of the shaft.

The cortical bone was relatively thick and the haversian canals were relatively small. On either side of the line of fracture corresponding to the area denuded of periosteum the bone was dead, as shown by vacant lacunae. Here the bone had undergone rarefaction by ingrowth of vascular tufts from subperiosteal and medullary sides. The haversian spaces were irregular in outline and showed various stages of bone rarefaction and bone production. In some of these there was little more than vascular tufts supported by reticulo-areolar tissue. In others there was a layer of osteoblasts on the surface of the bone; here new bone was being deposited, and a sharp line of demarcation existed between the old and new bone. On the whole, osteoblasts were abundant; in some areas a moderate number of osteoclasts were present, and in these areas

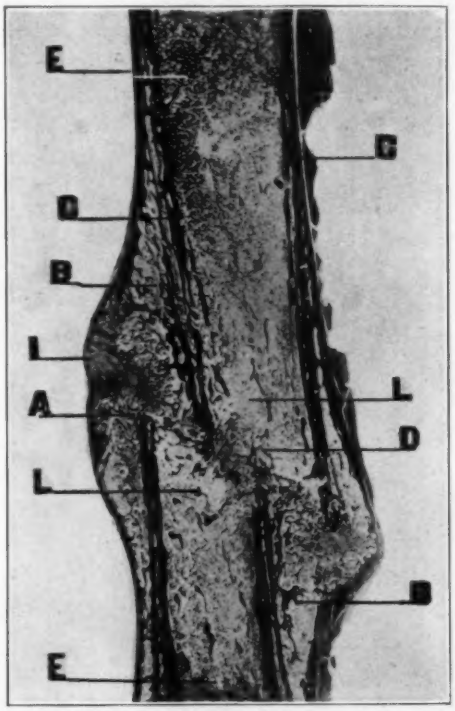

Fig. 21 (Kitten 16).—Longitudinal section at site of fracture of humerus; the duration of the experiment was thirty-four days. *A*, line of fracture with displacement; *B*, subperiosteal callus; *C*, cortex (rarefaction); *D*, medullary osseous callus; *E*, lymphoid marrow; *I*, cartilaginous callus, and *L*, region of fibrous marrow.

the spaces were very irregular in outline, with scarcely any evidence of bone production. The marrow in the area of fracture was fibrous; further away it was lymphoid and fatty.

The periosteum was thick and quite cellular. It had been lacerated and lifted off the cortical bone for a considerable distance on either side of the fracture line.

The subperiosteal callus was abundant and had for the most part undergone ossification. The older portions of the callus were seen in the angles between the raised periosteum and the cortical bone. As the fracture line was approached, many of the trabeculae were more or less cartilaginous and new

bone was being deposited on them, while at the level of the fracture line there was a thin band of cartilage which was undergoing ossification about ingrowths of vascular tufts from the marrow spaces of the osseous callus. The surfaces of the trabeculae were covered by osteoblasts. The subperiosteal callus was firmly united to the cortical bone and a sharp line of demarcation was visible between the two. This callus was continuous at the fracture line with the internal or medullary callus.

The medullary callus was osseous and extended across the bone at the level of the fracture. The trabeculae were covered by osteoblasts and were surrounded by quite cellular and vascular fibrous marrow; the blood vessels were large and engorged with blood. It was undergoing ossification. Trabeculae extended across the medullary portion of one of the fragments; from the marrow spaces, blood vessels were pushing their way into the fibrous tissue, cartilage was being deposited and this in turn was being replaced by bone. The new-formed trabeculae were covered by osteoblasts; new bone surrounded fragments of dead cortical bone; osteoclasts were moderately abundant on the surface of the trabeculae and were irregularly distributed. The marrow was for the most part fibrous; farther away it was lymphoid in character.

COMMENT

From the study of the histologic findings and illustrations of the foregoing experiments, we present the following comment on the healing process following simple fracture.

From the sequence of phenomena in the healing of simple fractures, it appears that the process of repair may be divided into periods, namely:

1. Period of inflammatory reaction and exudation.
2. Period of absorption of the inflammatory exudates and beginning repair.
3. Period of repair and readjustment.
4. Period of resolution or return to normal.

It is a fact that each period overlaps the one that precedes and follows and that the phenomena incident to each varies in degree according to the peculiarities and state of the individual organism as well as the environmental conditions. It has been observed that fibroblastic proliferation may begin before the third day in some, and that in others there is an apparent retardation until as late as the fifth day, the age of the animal—young or old—having much to do with the amount of injury done to the bone, apart from the character of the mechanism of production and conditions attending it.

From the foregoing experiments it is seen that following the simple fracture of a long bone in the kitten, there is a sliding and lifting up or separation of the periosteum from the cortical bone for varying distances, but rarely with complete laceration. The laceration is greatest in cases of displacement. In buckling fractures it may be stretched or ruptured on the side opposite to angulation (tensile stress) or it may be loosened to a greater or less extent from the cortical surface; while on the side of

angulation (compressive stress) it is loosened and relaxed. In some instances the separation of the periosteum under tensile stress appears to extend for a considerable distance from the fracture line, even nearly the whole length of the diaphysis (Kitten 3), as shown by the subperiosteal callus that is laid down. Where the periosteum is lacerated the ends retract more or less and may become widely separated, in part as the result of mechanical violence and in part from its inherent elasticity.

The sharp end of one fragment may pierce the periosteum, leaving an incomplete cylinder of periosteum uniting the two fragments.

Following solution of continuity of the cortical bone there is laceration of and hemorrhage from the vessels of the periosteum, haversian canals and marrow; the blood extravasates beneath the periosteum, between the fragments of the cortical bone and for varying distances into the medullary portion of the bone, and when there is laceration of the periosteum, blood escapes into the surrounding soft parts.

Coagulation of the blood occurs; the lacerated vessels become occluded by thrombi, and the clot fills the space between the lifted up periosteum and the cortical bone, between the ends of the fragments and for varying distances along the medullary portion of the fragments on either side of the fracture line.

The clot in these various positions is for the most part continuous, and serves as a temporary bridge between the fragments. In some of the specimens, however, there is a clear space between the fragments apparently filled with serum in the recent state.

The fibrin of the clot appears to be a natural stimulus to fibroblastic proliferation for, within a few days (three and one-half days in Kitten 1), fibroblastic and endothelial cell proliferation is seen to spring from the smaller vessels of the marrow especially along the inner surface of the cortical bone, and from vessels of the haversian canals on the external surface of the cortical bone and the inner surface of the periosteum.

This granulation tissue continues to develop, invades and finally replaces the clot, so that one sees in the early stages of the healing process following fracture varying amounts of granulation tissue and blood clot. As the process continues, the granulation tissue becomes more abundant and the clot gradually disappears.

The procallus granulation tissue develops from the vessels of the periosteum, haversian canals and marrow, and with its continued development the capillaries of the subperiosteal and medullary granulations of each fragment fuse so that the vascular communication is reestablished between the fragments. At an early period, osteal fibroblasts at the periphery of the formed clot begin to proliferate along the capillaries and to deposit fibrils and intercellular chondromucin so that osteoid material or cartilage is formed.

It has been observed that the manner of branching and the position of the blood vessels determine the form, position and manner of continuity of the early osteoid trabeculae. The trabeculae appear to be invariably laid down at a given distance from the blood vessels, the distance being in direct ratio to the size of the vessels. This also determines the form and the branching of the haversian canals. The final arrangement of bone trabeculae is dependent on function stress.

In the subperiosteal region, in the angle between the lifted up periosteum and the cortical bone, osteoid material makes its appearance early. As we approach the fracture line, the callus becomes more and more chondroblastic in character, while at the fracture line the callus is wholly cartilaginous. The cartilaginous callus here is removed by vascular erosion and replaced by osteoid trabeculae which gradually become osseous. As a rule in the medullary region, however, no chondroblastic tissue is deposited; the osteoid trabeculae develop

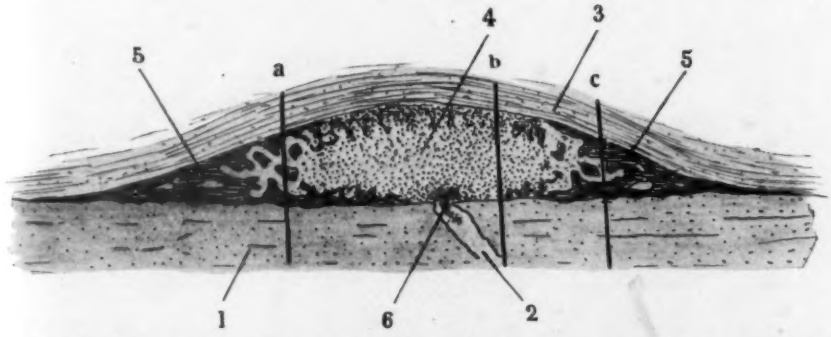

Fig. 22.—Parts of the subperiosteal callus about a fracture (comparison should be made with Figure 13); 1, compact tissue of diaphysis; 2, line of fracture; 3, periosteum; 4, central chondroblastic portion of the callus; 5, new bone formation; 6, fibrin and remains of blood clot. The region *a*, *b* and *c* is shown in Figure 23.

directly from the fibrous callus. Rarely, however, cartilage appears in the medullary region. The cellular activities within the marrow cavity are coincident with those in the subperiosteal region.

With the appearance of osteoid trabeculae, the precedent osteoblasts come more into evidence and form a line on the surface of the trabeculae. Ossification now becomes a prominent feature in the healing process. It has been noticed that no sooner are some of the trabeculae formed than their modification or removal begins—readjustment in response to an inherent progressive change. From the time of the first evidence of beginning absorption of the inflammatory exudate, osteoclasts rapidly increase, but not in the same degree in the different fractures; they appear to be particularly concerned in the removal of osseous fragments

and dead bone at the ends of the major fragments (Kitten 8). These giant cells are mainly concerned with the older trabeculae and matured bone. The early osteoid tissue, fibrocartilage and cartilage are mainly removed by vascular erosion.

During a certain period of repair, which varies as regards time in the different fractures, osteoclasts are exceedingly abundant. This is during the time when rarefaction is at its height. The activity of osteoclasts is indicated by the roughened surface of the original cortex and

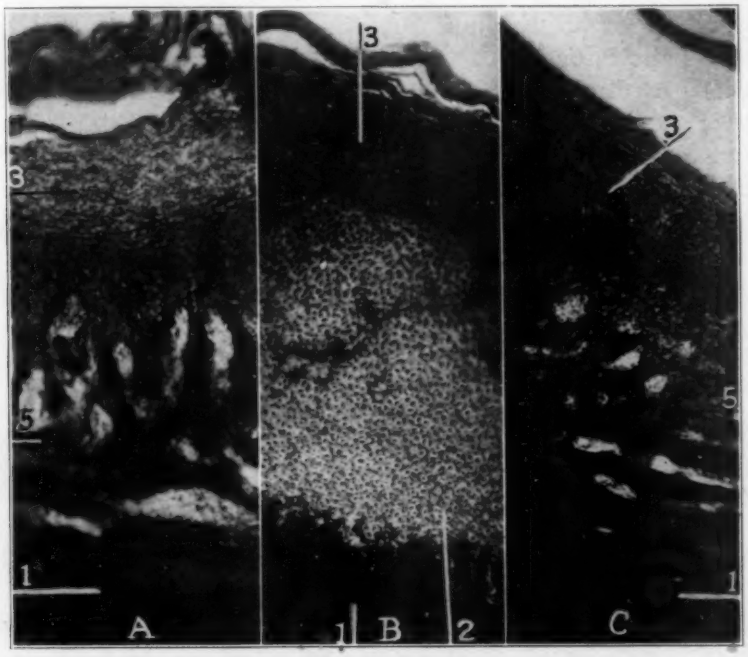

Fig. 23.—Portions of photomicrograph of longitudinal section of a healing fracture at the seventeenth day. 1, Compact tissue of diaphysis; 2, young cartilage (chondroblastic); 3, periosteum; 5, new bone formation (subperiosteal); *A* and *C*, through the peripheral third of the oval callus surrounding the point of fracture; *B*, through the lateral third of the central area of the callus (Fig. 22); hematoxylin and eosin.

detached fragments. The roughened surface is due to the so-called Howship's lacunae and at some period or other these are occupied by osteoclasts. The activity of these cells can be seen to have extended nearly the entire length of the diaphysis in some cases (Kitten 2), and it is particularly noticeable in cases of buckling fractures, in which loosening of the periosteum has occurred and the cortical bone has become necrotic. In these fractures areas of empty lacunae can be seen throughout the greater part and length of the diaphysis.

It appears to us that osteoclasts have a period of maximum activity. They entirely remove very small osseous fragments, nearly remove others, and only partially remove and roughen the surface of the larger ones. They suddenly become reduced in numbers—to a minimum, when osteoblasts appear in immense numbers and deposit osteoid material on the more or less roughened surface of the fragments and over the end of the major fragments. The new bone is thus mortised to the old and a sharp line of demarcation is seen between the two. Occasionally, separation occurs along this line, the interval (line of fracture) between the major fragments (cortical ends) being, as a rule, the very last to be bridged across.

As the osteoid tissue is formed the osteoblasts become buried in it and occupy the spaces or lacunae, and as the bone salts are deposited, well defined trabeculae extend in different planes. The bone cells of these new-formed trabeculae are large, as well as the osteoblasts on the surface of the trabeculae, and they stain well. In certain areas one sees these osteoblasts depositing lime salts about them, forming lacunae. This process occurs both in the subperiosteal and in the medullary regions.

As ossification proceeds new bone is deposited along the under surface of the raised periosteum or along the cortical bone on both surfaces, with areas of procallus granulation that have not as yet undergone ossification between the two, blending with the preforming chondroblastic callus (Figs. 12 and 13).

In many specimens the first portions of the subperiosteal callus to ossify are those next to the cortical bone, but in some few instances the ossification seems to begin against the periosteum. This seems to depend on the number of osteal fibroblasts that adhere to the cortical bone or periosteum.

In some specimens the periosteum separates from the cortical bone external to the fibro-elastic layer, thus leaving practically all the osteal fibroblasts adherent to the bone; in others the line of cleavage is flush with the cortical bone, with the osteal fibroblasts remaining attached to the elevated periosteum; while in others the line of cleavage is in the central portion of the fibro-elastic layer, and varying amounts of osteal fibroblasts remain attached to the periosteum and to the cortical bone.

The central portion of the subperiosteal callus at the line of fracture is the last to become ossified; here, cartilage is seen undergoing ossification by an ingrowth of blood vessels from the surrounding fibrous and osteoid callus, which results in absorption of the cartilage and formation of new trabeculae.

This delay in ossification is always found at the line of fracture, where the subperiosteal callus is of greatest thickness; tardy ossification may be due to the greater extent of the callus, which serves in a way as

an index to the degree of mobility, which Nature has to overcome, at this point.

A contributing cause for this delay in ossification may be the following: It is always found where the periosteum has been lacerated. In the earlier specimens one sees a definite laceration of the periosteum with the lacerated ends on the same level; in other and later specimens one sees the lacerated ends of the periosteum embedded in cartilaginous callus and lying at different levels; while in still later specimens a new periosteum has formed over the defect, and this can easily be distinguished from the original periosteum.

It would therefore appear that this delay in ossification is the result of abnormal mobility and disturbed blood supply at the line of fracture and in the area of laceration of the periosteum.

The medullary procallus granulations undergo a similar ossification without intermediate cartilaginous stage, and here new bone is deposited along the inner surface of the cortical bone and in the region of the fracture line across the medullary canal and across the line of fracture, uniting the fragments.

In a number of instances cartilage cells appear in the medullary callus, especially when there is considerable displacement of the major fragments followed by faulty alinement under treatment; this is particularly true, also, if the ingrowth of fibrous tissue takes place from the lacerated outer fibrous layer of the periosteum.

In specimens in which cartilage is present in this region there is always considerable lateral displacement of the fragments so that the cortical bone of one fragment lies in contact with the medulla of the other. It appears that pressure on the developing calluses plays an important part in the formation of cartilage.

Simultaneously with the organization of the blood clot by granulations springing from the periosteum, haversian canals and marrow, there are changes in the cortical bone following fracture, and with the occlusion of the vessels of the haversian canals by thrombi, there is death of the bone cells of the cortical bone for varying distances on either side of the fracture line.

This was shown by vacant lacunae in the cortical bone. The cortex when subjected to strain fractured in several ways: (1) In some there was a complete fracture, transverse or oblique with lifting up of the periosteum in the form of a cylinder or with laceration on one side; (2) in others the cortical bone buckled on one side, the opposite side remaining intact; (3) in still others there was considerable longitudinal fissuring and fragmentation, so that the ends of the fragments were often curled up or bent inward toward the medullary portion of the bone.

In older animals with complete fracture the periosteum is ruptured to a greater or less extent, according to the degree of violence and amount

of displacement. Force just sufficient to fracture the bone without displacement may result in very little injury to the periosteum, mere longitudinal laceration or rupture of bundles of fibers. In such cases a minimum amount of injury has been done, especially as regards the bone cells. Such an injury calls for a minimum amount of repair. Marked displacement and extensive laceration of the periosteum determine the other extreme (Kitten 18).

Repair and destructive changes—condensing and rarefying processes —go hand in hand until complete readjustment or return to normal is attained. The final stage of repair is completed when the external or subperiosteal callus becomes reduced to a miniumum (cicatrix) and the medullary callus is likewise removed and the cavity opened up with restoration of the continuity of the marrow. The latter may not occur if there has been marked or extreme displacement. In the later stages of repair, the lymphoid marrow becomes abundant and follows up the disappearing temporary internal callus.

It is to be recalled that in the initial stages of repair immediately following the injury the lymphoid marrow retreats well beyond the line of repair.

A buckling fracture implies a certain amount of inherent elasticity, such as is found in very young or adolescent animals and those suffering from malnutrition. In the production of fractures, a buckling was indicated by a sense of gradual yielding of the bone with or without a slight audible snap. The mechanism of yielding to a bending force has been studied independently of the series under consideration on bones removed from young animals after death. The bones were stripped of the surrounding muscles and fasciae and then submitted to bending across the thumb, as was done in the simple fractures under discussion. In each case the bone doubled up as any moderately elastic object would have done. As the bending was continued the diaphyseal cylinder flattened transversely to the long axis of the bone with longitudinal fissuring of the cortex at the sides; the fissures were usually relatively short.

The intervening marrow undergoes laceration and is forced extremityward in the medullary cavity. On the side of angulation buckling took place or, less often, the cortex fractured on the side opposite in true greenstick style.

In discussing the degree of injury produced in fracture of a long bone it is necessary to recall the histologic structure of the bone. The cortex of the diaphysis of long bones in young animals is relatively soft and elastic. The haversian systems consist of concentric lamellae running in different directions and branching in different planes.

Interposed between the lamellae are the lacunae, containing the bone cells, and radiating from the lacunae and connecting them are the canaliculi containing the protoplasmic processes of the bone cells.

These young bones contain a relatively and absolutely greater amount of organic matter than the bones of older animals and therefore bend, buckle, fragment and fissure to a greater extent than the bones of older animals.

It is obvious that during the mechanism of bending the lamellae affected would be tightly compressed one against the other, with crushing of the interposed bone cells; the bending stress affects with greatest force the lamellae at the line of acute angulation, diminishing thence toward the extremities of the bone.

The injury to the bone cells can readily be recognized and traced to a greater or less extent in the sections of all of the fractures studied in the present series. The amount of injury to the bone cells varies according to the degree of elasticity of the diaphysis. In very flexible and elastic bones, the dead cells (vacant lacunae) can be followed in irregular areas nearly the whole length of the diaphysis in some instances.

In older animals in which there was less organic material and hence less elasticity, the bone gave way suddenly under stress and fractured in one plane. In these the vacant lacunae were observed only in the immediate vicinity of the fracture line.

The amount of injury done to the cortical bone, as indicated by vacant lacunae in the present series of simple fracture in young animals, was very remarkable.

The dead bone gradually undergoes absorption by cellular and vascular erosion, and the necrotic cortical bone or loose fragments of the latter and the trabeculae of the medullary portion are gradually absorbed.

The surface of the dead bone becomes irregular and "moth eaten." In some areas vascular tufts occupy these irregular spaces while in other areas abundant osteoclasts in Howship's lacunae are seen. As original haversian canals become enlarged, one notices the deposition of new osseous tissue along the walls of the enlarged haversian canals.

A very sharp line of demarcation is seen between the dead bone, the lacunae of which are vacant, and the new-formed living bone with well formed and well stained bone cells. The new bone is mortised into the dead bone.

When a certain degree of homogeneity between the ossifying callus and the rarefying bone has been attained, the new trabeculae, which lie in the lines of greatest stress or pressure, become more and more dense by a filling up of the vascular spaces with bone, while those which lie outside the lines of pressure are gradually absorbed. By this process much of the subperiosteal and most of the medullary callus is absorbed and a new cortical bone is formed, which bridges the area of fracture.

The marrow, originally lymphoid in character, in the kitten rapidly becomes delicate, highly vascular and edematous fibrous marrow, with the development of the medullary callus; this type of marrow is seen in the marrow spaces separating the new trabeculae. As union between the fragments occurs and the trabeculae outside the lines of pressure become absorbed, fibrous marrow is replaced by lymphoid marrow.

It must be kept in mind that the activities going on in any given fracture constitute a complex—constructive and destructive, general in part as well as local in scattered areas, the one area overlapping that of the adjacent areas, and so on until healing may be said to have been completed. Even under normal conditions of health, the physiologic activities are as complex, probably much less in degree, in response to stresses from locomotional and occupational demands. The salient facts and characteristics of each fracture of the series under discussion may best be presented by the following epitomized statements:

CONCLUSIONS

1. Age is an important factor in determining certain phenomena that occur at the time of injury and during the process of the healing of fractures.

2. The character of the mechanism of production determines and imparts certain characteristics to each fracture, according to age and environmental conditions attending each injury.

3. The bones of young animals yield to force by bending, buckling on the side of angulation from compressive stress, or fracturing on the side of tensile stress (true greenstick). The property of yielding to bending stress diminishes as age advances, as the result of increased deposition of earthy salts in the bones.

4. The bones of adults, when normal and subjected to stress, yield by sudden solution of continuity with resulting molecular shock, accompanied by more or less fragmentation.

5. The periosteum is more or less lacerated, or stretched and loosened from the surface of the diaphyseal cortex. This loosening or stretching is often quite extensive in fractures of the bones of young animals.

6. By compressive stress the bone cells are destroyed for a variable distance from the line of fracture. This injury is recognized by the irregularly distributed areas of empty lacunae in the cortex of the diaphysis.

7. Bone cells in the immediate vicinity of the fracture line are always destroyed and the ruptured blood vessels are closed by blood clot.

8. Empty lacunae signify dead bone. Fragments of bone show empty lacunae; these, as well as the dead bone of the diaphyseal cortex are more or less removed by osteoclastic activity.

9. Cartilage, fibrocartilage and osteoid tissue not permeated by earthy salts are removed mainly by vascular erosion.

10. After earthy salts have been deposited in osteoid tissue osteoclastic action is called for.

11. Osteoclasts, by the formation of Howship's lacunae, roughen the surface of the diaphyseal cortex and that of fragments preparatory to the deposition of fibrous and osteoid callus.

12. The deposition of fibrous or osteoid callus on the surface of the cortical bone so roughened secures firm interlocking or attachment between the old and the new bone. This interlocking of cortex and callus as a result of osteoclastic activity imparts marked resistance to stresses and minimizes the liability to cleavage or separation of the newly deposited bone or callus. The deposition of new bone or callus on a plane cortical surface would be a line of least resistance.

13. Bending stress when applied to healing fractures may bring about separation between the new bone and the old cortex. This has been observed in the experimental series.

14. Wherever periosteum is lifted up or loosened from the diaphysis of an injured bone, deposition of osteoid callus (osseous) takes place, the amount depending on the extent of separation; this deposition is usually preceded by cortical roughening by osteoclasts.

15. All reparative processes are modified by individual peculiarities; these included those of age, state of nutrition, function and environmental conditions.

16. When the periosteum is lacerated and the edges retracted it allows of the ingrowth of fibrous tissue from the outer layer. This tissue is not osteogenetic and it forms a barrier to osseous union of the fragments; sometimes this is overcome by pressure from functional use, which induces a metaplastic change in the tissue resulting either in osseous union or new joint formation (nearthrosis).

17. Cartilaginous callus usually does not appear within the medullary callus. This sometimes occurs, however, as the result of the ingrowth of subperiosteal elements which possess an inherent tendency to develop chondroblasts. This ingrowth is apt to follow in cases of comminution in which proper alinement is difficult or impossible.

18. Callus formation between the cortical ends of the major fragments is the last to take place; the interval is often filled from within and from without. An intermediate callus is an uncertain factor as coming from the ends of the cortical fragments.

CANCER OF THE SKIN*

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PART I

In the last twenty-five years, a great many instructive papers have been written on the various types of cancer of the skin. The majority of these contributions, however, have been made by specialists in some field of therapeutics, and consequently carry a certain amount of bias for a method of treatment. The controversies over the pathologic aspect of skin malignancies which enriched the literature at the beginning of the century have subsided, and that phase of the question appears to be settled. Hazen, in his "Skin Cancer," has presented the subject admirably, and has given us a reference book for the advanced student. No one else, so far as I know, has attempted to concentrate our knowledge simply and with an unprejudiced point of view, so that the medical student and practitioner, may have a brief résumé available.

It seems worth while, then, to consider briefly some of the pictures of cancer of the skin seen in the New Haven Hospital not only because the condition is so common, but also in the hope that physicians may be led to recognize the lesions in the earlier stages. Only in this way can the later disasters be avoided.

For practical purposes there are only three types of skin cancer, the basal cell, the squamous cell, and the nevoid and melanotic growths. The last group may be regarded as the most malignant because of its rapid dissemination but, in other respects, resembles the squamous cell cancers, and will not be included in this paper. Numerous other forms of interest to the special student fall, as far as behavior and treatment are concerned, into one or the other of these main groups. Typical examples of these neoplasms will be presented to illustrate the etiology, age, location, pathology, progress and treatment.

BASAL CELL CANCER; RODENT ULCER—JACOB'S ULCER; HAIR-MATRIX CANCER; "CANCROID"

HISTORY AND ORIGIN

Previous to the observation of Krompecher,[1] in 1900, which definitely separated the basal cell group from the others, there had been a great deal of confusion in classification. These tumors had even been regarded

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1. Krompecher: Beitr. z. path. Anat. u. z. allg. Path., 1900, p. 28.

as endothelial in origin by some, and "cancroid" was a term in common use at that time. Krompecher,[2] in a monograph (1903), amplified his original observation, and although a pathologic battle royal followed, his classification has weathered the storm and is generally accepted with some slight modifications at the present. Bloodgood [3] early appreciated the importance of Krompecher's point of view and became his strong supporter, adding the weight of his own cases to the evidence.

Borrmann [4] disputed the contention that these growths originated from the basal layer of the skin or its appendages, and asserted that they arose from subepidermal nodules, "cell rests," becoming attached to the rete pegs by secondary fusion; he showed, by serial sections, a great many cases in which there was no connection with the overlying basal layer.

On the other hand, Fordyce [5] made the assertion that the great majority of these tumors started in the epidermis covering the sheath of the hair follicle, and in this he had the support of Mallory,[6] who called them "hair-matrix" cancers. Janeway,[7] from a study of very early cases, was convinced that most of the cutaneous cancers were direct outgrowths from the normal epithelial cells, that the essential change was a degeneration that depended on the existence of a previously isolated group of cells (as Borrmann held), or was associated with lesions in the connective tissue in a second class (as Ribbert emphasized), but which, in a third and larger division, was based on metaplasia of the epithelial cells alone, with no changes whatsoever in the connective tissue. Today, it is generally conceded that basal cell cancer may arise in the basal layers of the skin, in fetal rests under the skin or in the hair follicles, sweat or sebaceous gland structures.

AGE, SEX, RACE AND OCCUPATION

Although growths of basal cell type may occur in young people, such a finding must be considered decidedly unusual. Broders [8] gave the average age of the Mayo Clinic patients with this condition as 56.7 years. Savatard [9] placed the maximum of the curve at the forty-fifth year. He reported a well defined rodent ulcer, however, in a patient of 17 years,

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2. Krompecher: Der Basalzellenkrebs, Jena, 1903.
3. Bloodgood, J. C.: Prog. Med., December, 1904, p. 134.
4. Borrmann, R.: Ztschr. f. Krebsforsch. **2**:1, 1904.
5. Fordyce, J. A.: The Pathology of Malignant Epithelial Growths of the Skin, J. A. M. A. **55**:1624-1631 (Nov. 5) 1910.
6. Mallory, F. B.: The Principles of Pathologic Histology, 1914, p. 371.
7. Janeway, H. H.: Ztschr. f. Krebsforsch. **8**:403-435, 1910.
8. Broders, A. C.: Basal Cell Epithelioma, J. A. M. A. **72**:856 (March 22) 1919.
9. Savatard, L.: Brit. J. Dermat. **32**:375 (Dec.) 1920.

and argued that almost as many rodent ulcers *began* between 17 and 45 years as between 45 and 80 years. Sweetzer [10] had 27 years and 86 years as the extremes of his series. Lain [11] claimed to have seen three patients under 30 years of age with basal cell cancer. Hazen [12] reported three people under 30 years of age, but the greatest number presented themselves between 50 years and 70 years. The majority of the New Haven Hospital group were in the age period from 40 to 80 years. The youngest patient (Case 13) had a growth of eight months', or more, duration at 24 years of age. Probably, the percentage of cancer of this type in very old people is high relative to the number surviving.

The sex incidence given by different writers is varied. It ranges from ratios of four males to one female to equal sex frequency. It would seem that there should be a larger number of males afflicted, owing to the bearing of exposure to sun, etc., which will be taken up later.

Opinion is unanimous that blondes are especially liable to develop basal cell cancer and that the dark skinned races have a relative freedom from it. For that reason the English, Scotch, Irish, Germans, Scandinavians and their descendants make up the nationalities of the patients affected. Hazen,[13] in spite of his residence in the south, has seen only four cases in the negro. He claims that the negro does not have senile keratoses, which is the most frequent precancerous condition resulting in the basal cell growths. Lain,[11] likewise, though living where he has opportunity to see large numbers of American Indians, has never seen a basal cell cancer in this race. The patients of the New Haven Hospital series were, with one exception, members of the northern races or descended from them. The exception was a very dark Italian with a typical basal cell growth at the inner canthus of the left eye. No Spanish, Greek, Hebrew, Armenian, Syrian or other Mediterranean nationality was represented.

In regard to occupation, exposure to sunlight and weather has a marked bearing. The occupation most hazardous from this standpoint is that of farmer. This is borne out in the statistics of McCoy,[14] who noted 93.5 per cent. in farmers or their wives, of Sutton,[15] whose figures were 72 per cent., and Broders,[8] who mentioned that farmers were more

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10. Sweetzer, S. E.: Skin Cancer, J. A. M. A. **69**:179 (July 21) 1917.
11. Lain, E. S., cited by Sweetzer (Footnote 10).
12. Hazen, H. H.: Roentgen-Ray Treatment of Cutaneous Cancer, J. A. M. A. **76**:1222 (April 30) 1921.
13. Hazen, H. H.: South. M. J. **10**:241 (March) 1917.
14. McCoy, J. N.: Solar Keratoses and Cutaneous Cancer, Arch. Dermat. & Syph. **1**:175 (Feb.) 1920.
15. Sutton, R. L.: Clinical Study of Carcinoma of Nose, J. A. M. A. **77**:1561 (Nov.) 1921.

often involved than others. Occupations such as carpenter, sailor, policeman and country doctor therefore also carry a risk when the exposure is continuous over a period of years. Frost bite of the ears and cheek has also led to development of basal cell growths according to Sutton.[16]

ETIOLOGY

Bloodgood [3] was early responsible for the statement that he had never seen this type of cancer arise in the normal skin. Nearly every writer on the subject has since supported this observation. The term "precancerous dermatoses" [17] has come into use to express the group of conditions supposed to represent the precursors of the cancer of the skin. Hazen [18] states that 2 per cent. of all the dermatoses are cancerous in nature. By far the most common antecedent dermatosis is the seborrheic wart, a lesion which is frequently seen in elderly people. These warts are slow-developing, slightly raised, yellowish to black areas, often covered with a greasy scale, which is usually closely adherent. They appear on the exposed skin and never completely heal at any time.

Many writers have commented on the relationship of chronic sunlight exposure to the development of senile keratoses and seborrheic warts. Dubreuilh [19] asserted that the causes of these senile changes are age and exposure to sunlight. He found keratoses much more frequently in country people than in city dwellers, and only on the uncovered parts of the skin. Thus, the face, dorsal surface of the hands and, rarely, the back of the neck and back of the forearm were the most commonly involved, whereas the chin, front of the neck, lower limbs and fingers, all of which are shaded, were never affected. Furthermore, a most remarkable demonstration was afforded by the fact that women who wore the "foulard" (a silk handkerchief about their heads), as part of their costume, never had keratoses develop under it, although the remaining portions of exposed skin of the face presented the lesions. Montgomery [20] confirmed these observations, and additional support has been added by Paul,[21] Hyde,[22] McCoy [14] and Sutton.[15] The condition known as xeroderma pigmentosum is an excellent example of the effect of light

16. Sutton, R. L.: Frostbite and Cancer, J. A. M. A. **69**:2171 (Dec.) 1917.

17. Highman: New York M. J. **116**:367 (Oct.) 1922. Bowen, J. T.: J. Cutan. Dis. **30**:241-255, 1912.

18. Hazen, H. H.: South. M. J. **8**:577, 1915.

19. Dubreuilh, W.: Ann. de dermat. et syph. **8**:387-416, 1907.

20. Montgomery, D. W.: Unusual Exposure to Light Followed by Seborrheic Keratosis, J. A. M. A. **60**:7 (Jan. 4) 1913.

21. Paul, C. N.: The Influence of Sunlight in the Production of Cancer of the Skin, London, H. K. Lewis & Co., 1918.

22. Hyde, J. N.: Am. J. M. Sc. **131**:1-22 (Jan.) 1906.

in the production of basal cell cancer. Fortunately, this distressing disease of young people is extremely rare. Other preceding skin dermatoses from which basal cell growths may arise are pimples, small subcutaneous nodules, eczema, and small scars or ulcers due to trauma.

Cases 2, 4 and 12 of this report illustrate origin in seborrheic keratoses; Cases 1 and 6, origin in "pimple"; Cases 8, 10 and 16, trauma from eyeglasses; Cases 14, 12, 11 and 9, trauma from other causes, including shotgun injury, horse kick and scratches; Case 18 arose in an eczema.

SEATS OF ELECTION

The most common situations for the development of basal cell growths are the nose, cheeks, and outer and inner canthi of the eyes. Broders [8] reported 96 per cent. above the clavicle, in his series, and Schreiner, Simpson and Müller [23] 90 per cent. on the face, all notably above a line on a level with the upper lip. Less commonly the temporal region, the forehead, the ears and the upper lip are involved. The chin and front of the neck are rarely the seats of election. Sometimes these cancers occur on the extremities and trunk, but it is unusual. The nose is the site of predilection, especially at the alar furrow, the nasofacial fold and the bridge. Sutton [15] gave a report of fifty of these nasal cases. If we were to consider the face as a target, it would be evident that the basal cell cancers occupy mainly the center of the bull's eye (nose, cheeks and eyes) with scattering hits around the periphery. The cases included in this report have been selected to show the situations involved by basal cell cancer (Cases 1 to 20).

PATHOLOGY

In appearance the growths may be flat, nodular, ulcerative or annular, healing in the center and progressing on the periphery. Characteristics of all, however, are the induration and the hardness of the edges that, in some cases, gives the edge a rolled, heaped up effect. Careful examination of the edge will usually reveal translucent, pearly white nodules, which are pathognomonic of the rodent ulcers. When the nodular type has reached a certain size, ulceration is nearly certain to follow. The ulcers are covered with yellowish crusts, scabs or dry scales, or by a pale, unhealthy looking, thin granulation tissue. There is usually exudation of a yellow serous material. The annular type is very infrequent. It is termed "morphea-like" by the dermatologists, and is characterized by a whitish yellow healed central area surrounded by a ring of either raised pearly edged growth or scabbed ulcerations with

23. Schreiner, B. F.; Simpson, B. T., and Müller, T.: Am. J. Surg. **33**:1 (Jan.) 1919.

teleangiectatic vessels coursing toward the center. These morphea-like basal cell cancers have been reported by Hartzell [24] and Heidingsfeld,[25] who reviewed the literature. Case 8 is a representative of this rare type. Cases 3, 12 and 13 are examples of the flat, nodular and ulcerative forms. Certain scarlike basal cell cancers and other forms [26] are so rare that they need not be considered here.

There is a tendency to multiplicity of the basal cell cancers, the origin being from distinct centers, according to Petersen.[27] This has been proved by serial sections and wax model reconstruction. Cases 14, 15 and 16 illustrate this point. A fact of considerable importance is that the growth under the skin is much more extensive than the surface appearance indicates. This necessitates a good margin for excision and a wide area for radiotherapy.

On section in the gross, the basal cell cancer is characterized by a smooth surface, a limited invasion of the subcutaneous tissues and by alveoli which are much smaller than the squamous cell growths, so small in fact that they are often indistinguishable. The squamous cell cancer has a rough surface, deep infiltration and alveoli radiating downward in the form of white lines about the size of a very fine thread.[28]

Microscopically, the cells partake of all the staining qualities of the basal layer of the skin. The cells are small, closely packed, with dark blue, round or elliptical nuclei and lighter blue cytoplasm, so that they make excellent microphotographs. Hazen shows some beautiful examples of the very earliest changes in his book. After the corium is invaded, the cells vary greatly in arrangement. They may be gathered in solid masses, in branching outgrowths, in hollow columns with almost an adenomatous appearance, in cystlike structures, or in irregular thin strands interspersed with connective tissue. Figure 22 gives examples of the varied pathologic types. Mitotic figures are easily found in the basal cells and degenerating forms, the latter also being present in the spinous cells above them. A very striking feature of the picture is the invasion and walling off process in which small round cells take part. These cells comprise not only the lymphocytes, but also plasma cells and fixed tissue cells, and there is an accompanying fibrous tissue reaction.

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24. Hartzell, M. B.: Morphea-Like Epithelioma, J. A. M. A. **53**:262-264 (July 24) 1909.

25. Heidingsfeld, M. L.: J. Cutan. Dis. **31**:379-383. 1913.

26. Ketron, L. W.: J. Cutan. Dis. **37**:22 (Jan.) 1919. Milian: Ann. de dermat. et syph. **4**:845-847, 1903.

27. Petersen: Beitr. z. klin. Chir. **32**:543, 1902.

28. Hazen, H. H.: Prickle Cell and Basal Cell Skin Cancers, J. A. M. A. **64**:958 (March 20) 1915.

SYMPTOMS AND CLINICAL COURSE

Most of the patients present themselves for treatment, not because of symptoms but in order to be rid of a sore that will not heal or is growing larger. In other words, the symptoms are relatively trivial. At times, however, there is an itching or irritating sensation; at other times, bleeding or discharge, which may be serous or purulent, if infected. In a few instances there is a complaint of real pain.

The clinical course is that of chronicity. The lesion is neglected because the progress is so slow that the patient does not worry about it. The growth may be a year or more in reaching the size of a dried pea (0.5 cm.). Ulceration, when it takes place is masked by scaling over of the area, the scab coming away at times but reforming soon afterward. At the end of ten or fifteen years, there may be a cancer only the size of a 25 cent piece. This is not always the case, however, as there is considerable variation in the growth rate in different persons. There are several possibilities that may occur. The progress may be one of slow invasion of the underlying tissues, neither cartilage nor bone being spared in the march. This gnawing out and erosion of healthy structures has earned the title of "rodent ulcer" for these growths. Cases 17 and 18 are good examples of the rodent ulcer tendency. Or, secondary infection takes place and death comes, as a rule, from this or hemorrhage; or, finally, there may be a fungating, sloughing mass of tissue when subcutaneous invasion is prevented.

There is a chance that the basal cell cancer may be changed into a more rapidly growing form or even transformed into a squamous cell type if inadequately treated by any method,[29] and sometimes this change occurs spontaneously where no treatment has been used.[30]

The statement is often made that basal cell cancer never metastasizes. Körbl [29] reports two such cases and refers to a similar case of Lexer's; Hazen [13] gives four more examples, and Finnerud [31] adds two cases of his own and one case which he accepted from the five case reports he found in the literature. Some authorities would probably consider all the foregoing cases to be examples of cubocell cancer.

In actual practice, then, the basal cell cancer is to be regarded as a relatively benign growth. It tends to remain localized, is very slow in developing, metastasizes so rarely that it is exceptional, and kills by eroding and invading the tissues about it, thereby causing infection and hemorrhage.

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29. Körbl, H.: Arch. f. klin. Chir. **97**:752-816, 1912.

30. Davies: Brit. J. Dermat. & Syph. **34**:145, 1922. Broders (Footnote 8).

31. Finnerud, C. W.: Metastatic Basal Cell Carcinoma from Skin, J. A. M. A. **82**:775 (March 8) 1924.

DIAGNOSIS

The diagnosis is made from the age, location, origin, appearance, evolution, radiosensibility and microscopic section, if necessary. A slow-growing, hard, painless, bluish white, nodular sore, arising in a previously unhealthy skin patch and occurring on the face of an old person, is more apt to be basal cell cancer than anything else. If, on application of radiotherapy, there is a decided response within the proper time, the diagnosis is almost certain.

Conditions most necessary to be differentiated from basal cell growths are the following:

A. *Squamous Cell Cancer.*—The very early pin-head sized squamous cell growths cannot be differentiated; but the evolution is so rapid that, in three weeks or three months, squamous cell cancer reaches a size that basal cell growths attain only after years; also, the induration is more marked and the infiltration of the true skin more apparent. The distribution of the squamous cell cancer quite frequently on the extremities and genitals and at the mucocutaneous border of the lip, as well as on the face, are further points to be considered.[9] There is also the enlargement of the regional glands when metastasis has taken place in squamous cell cancer.

B. *Syphilis.*—A primary extragenital chancre must always be thought of when the patient is young, has a rapidly developing hard nodule that may ulcerate, and enlarged regional glands. It is much more often necessary to differentiate chancre from squamous cell than from basal cell cancer. Examination of scrapings under the dark field microscope may be of great value. Tertiary syphilis, however, may closely simulate a rodent ulcer. Usually, other signs of syphilis are present, but, these failing, the character of the ulceration, the tendency to inflammation about the edge as well as the absence of pearly nodules and induration, the presence of the other scars in the vicinity, and the history of painful progress may be of assistance. The blood Wassermann reaction, a piece of tissue for microscopic examination, or therapeutic administration of antisyphilitic drugs will often decide the question. Case 21 shows an example of this kind.

C. *Lupus Vulgaris.*—This can be differentiated by its origin in a young person, irregular outline with occasional healed red scars, and the overhanging edge of the ulcer. There is no induration present, and pressure with a glass slide shows the apple jelly appearance considered pathognomonic.

D. *Lupus Erythematosus.*—This appears as a pink scar on the face, extending in scattered patches around the nose, cheeks and ears. There

are no signs to make one think of rodent ulcer, as there is no ulceration or characteristic edge.

Other dermatologic conditions occasionally confused with cancer of the skin are granuloma pyogenicum, blastomycosis, morphea and simple inflammations.[32]

TREATMENT

Prophylaxis is of the greatest importance, and much can be done to prevent the development of cancer by attention to the precancerous dermatoses. The keratoses are best removed by electrocoagulation, as they require an erythema dose of roentgen rays or radium; warts and moles may respond to either of the latter agents as well.[33] The eradication of these skin blemishes has been urged by Eastman.[34]

It is the basal cell cancer that has established the reputation of the cancer quack. For years cures have been realized by any one of a number of methods. The fact that this form of cancer is relatively harmless in a majority of instances has allowed the trial of a large assortment of remedies. It is surprising to see, in the literature, the reports of methods of treatment that have been tried successfully in this condition. Cures have been reported by the use of various free acids [35] and caustics; by freezing with carbon dioxid snow; by treating with steam; [36] by exposure to sunlight; [37] by use of the Finsen light; [38] by injection of fluorescent substances (eosin, etc.) and exposure to sunlight or the carbon arc; [39] by the burning glass; [40] by arsenous oxid paste; [41] and by acid nitrate of mercury.[42] Not one of these treatments would be advocated by any of the leading men today, because there are other better means of dealing with the problem.

Today, we have a choice of methods any one of which can be used successfully in a majority of instances. Treatment by any method, however, should be thorough and carried out by an expert in the work he is undertaking. The treatment of choice will depend largely on the conditions found in each individual case, and also on the technical ability

32. Hazen, H. H.: South. M. J. **9**:790 (Sept.) 1916.
33. Pfahler, G. E.: New York M. J. **116**:553-555 (Nov.) 1922.
34. Eastman, R.: Prophylaxis of Malignant Growths of the Mouth, Face and Jaws, J. A. M. A. **79**:118 (July 8) 1922.
35. Weinbrenner: München. med. Wchnschr. **61**:127, 1914.
36. Gillette, W. J.: M. Rec. **89**:65 (Jan. 8) 1916.
37. Hirschberg, M.: Berl. klin. Wchnschr. **42**:1310-1312, 1905.
38. Schlasberg, H. S.: Arch. f. Dermat. u. Syph. **78**:163-184, 1906.
39. Jesionek, A., and von Tappeiner, H.: Deutsch. Arch. f. klin. Med. **82**:223-227, 1905.
40. Seelye, H. H.: New York M. J. **99**:279, 1914.
41. Robinson, A. R.: M. Rec., 1900, p. 355.
42. Sherwee, S.: New York M. J. **8**:304-308, 1908; J. Cutan. Dis. **29**:594, 1911.

obtainable. For instance, it is much better to have the growth removed by a good surgeon than mishandled by a poor radiotherapist, or vice versa.

There are two forms of therapy which must be carefully considered: radiotherapy, which includes roentgen ray and radium, and surgery, which includes knife excision, cautery excision and desiccation, or monopolar endothermy.

RADIOTHERAPY

For the early and unmistakable basal cell lesions, radiotherapy is indicated. The results are equally favorable with either roentgen rays or radium. Cases 1 and 2 illustrate this fact well. At the same time, it would be futile to deny the ease and good results of surgical excision in small accessible lesions, procain anesthesia being used. Case 13 is a good example. Radiotherapy has had a good trial and is no longer in the experimental stage. There is very little difference in the action of roentgen rays and radium, and the selection of one over the other is merely a matter of convenience. Radium can at times be applied more accurately, thus assuring an equality of radiation, especially in such situations as the inner canthus, where the roentgen rays treat the surrounding high points more intensely than the growth. Small apertures like the nostril or external auditory canal also are readily treated by radium and with great difficulty by roentgen rays. A cross fire effect on growths on the nose can be obtained by use of radium in the nostril and roentgen rays externally. There is no necessity for extensive screening of the normal skin when radium is used; this adds to the comfort of the patient. The patient is spared the noise of the machine, the dimly lighted, depressing atmosphere of the average roentgen-ray treatment room, and, when the radium is once in place, there is no necessity for remaining in a fixed position. The time may then be passed pleasantly reading or talking with friends. Occasionally, a growth is found which proves refractory to roentgen-ray treatment, and which yields readily to radium. The reverse is not true.[43] The roentgen rays, on the other hand, can be used to cover a more extensive surface in a much shorter time. The two forms of treatment may often be combined profitably.

In the very late cases in which there is deep ulceration, sloughing and involvement of underlying cartilage and bone, any form of radiotherapy may have very little effect, in some instances. This fact is recognized by practically all the leading radiotherapists and dermatologists. Pfahler [33] says:

> When the disease has invaded the deeper tissues and especially when it has extended to cartilage or bone, the outlook is much more grave; the amount

43. MacKee, G. J.: Am. J. Roentgenol. **6**:119 (March) 1919. Green, R. A. A.: Lancet **1**:544 (April 7) 1917.

of treatment required is greatly increased and even after long struggles failure will be common.

MacKee [43] emphasizes the difficulty in treating eyelid cases, and Sutton [44] finds the ear equally hard to treat when the cartilage is attacked. Hazen,[12] Grier,[45] Quigley,[46] Morrow and Taussig [47] and others have added confirmation to this point.

Cases 17 and 18 are examples of invasion of nasal cartilages which were not influenced by radiotherapy. Case 6 shows involvement of the lower eyelid, which needed surgical excision for permanent healing.

The technic of application of radiotherapy varies with the extent of the lesion to be treated and manifestly cannot be taken up in this paper. There are certain rules, however, that are now generally accepted. The attack should be made in as few intensive treatments as possible. It is preferable to get rid of the condition in one treatment,[48] avoiding the Scylla of ulcerative radiodermatitis on the one hand, and the Charybdis of relapse on the other. A first degree radiodermatitis is the aim of most radiotherapists, the earlier failures probably representing incomplete radiation. A second course of treatment can be undertaken after a three weeks' interval, if the first dose has been properly given. It is as essential to give a margin to the growth in treatment by radiotherapy as in surgical excision. In superficial growths, no filters or a very thin filter [49] may be used; in deeper growths, filtration is necessary to get proper penetrating rays into the tissues and to cut out the longer, more caustic rays which cause skin burns. A growth that does not respond to radiotherapy after two or three trials should be treated by some other method.[43]

The disadvantages of radiotherapy to be considered are: acute radiodermatitis of severe grade; subsequent wrinkling, teleangiectasis and chronic radiodermatitis; depilation of eyelashes and conjunctivitis when used near the eye, and recurrence. In expert hands there is very little danger of acute radiodermatitis or the sequelae. Depilation of the eyelashes and conjunctivitis are, however, very real and scarcely avoidable,

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44. Sutton, R. L.: Carcinoma of External Ear, J. A. M. A. **74**:88 (Jan. 10) 1920.

45. Grier, G. W.: J. Radiol. **2**:39 (Nov.) 1921.

46. Quigley, D. T.: Am. J. Roentgenol. **10**:161-162 (Feb.) 1923.

47. Morrow, H., and Taussig, L.: Am. J. Roentgenol. **10**:212-218 (March) 1923.

48. Clark, A. S.: Radium Treatment of Cutaneous Epitheliomas by Single or Massive Doses, J. A. M. A. **62**:1453-1458 (May 9) 1914. MacKee (Footnote 43). Green (Footnote 43).

49. Remer, J., and Witherbee, W. D.: New York M. J. **112**:935 (Dec.) 1920.

making it debatable whether the desiccation method of Clark [50] is not to be preferred when the endotherm is available. Recurrence may take place even when radiotherapy has been applied by the most expert. Most recurrences take place between six months and one year after treatment, and, if the year elapses without recurrence, a permanent cure is probable. The return of the growth may be in the center, at the edge, or in the depths of the treated area. MacKee [43] reports 15 per cent. recurrence in 201 cases and Hazen [12] 7 per cent. recurrence in 147 cases. These relapses respond better to massive treatment than to the former fractional technic, and a clinical cure may be obtained by a second or third treatment. The cases that do not respond should be treated by other methods. Case 5 shows the depilatory effects on the lower eyelid from a radium treatment years previously. Cases 5, 6 and 17 represent relapses following radiotherapy. The danger of relapse imposes the duty of a very careful follow-up in every patient treated by radiotherapy.

When radiotherapy is successful, the cosmetic result is usually very good. The scars are pliant, and not easily discernible. At times when ulceration has been marked, the scarring is quite conspicuous. The results obtained by roentgenotherapy are as favorable as from any other therapy. MacKee [43] got 90 per cent. clinical cures in his series, and, omitting the cases hopeless from the start, nearer to from 96 to 98 per cent.; Simpson [51] claims that failure to bring about recovery in over 200 cases has been rare. Schreiner, Simpson and Müller [23] had 97 per cent. success with roentgen-ray treatment and 50 per cent. with radium. The large radium institutes give excellent reports, in this condition, from the use of radium.

It is often stated that there is a selective destructive action on the cancer cells when radiation is used. A true example of selective destructive action is the effect on the mucosa of the normal intestine [52] or the circulating lymphocyte.[53] Here the effect is immediate and at its height within from one to two days after radiation. There is no comparable picture in radiated basal cell growths. It often requires two weeks before the slightest change is observable, and then the neoplasm slowly disappears. This phenomenon seems more like the building up of a resistance that causes the downfall of the injured cells when the proper level is reached. This conception fits well with the pathologic picture observed after radiation. According to Marschalkó [54] there is a reactive inflammation with thickening of the epithelium, infiltration of the tissues

50. Clark, W. L.: Desiccation, J. A. M. A. **67**:17 (July 1) 1916.
51. Simpson, F. E.: Radium, J. A. M. A. **67**:1508 (Nov. 18) 1916.
52. Whipple, G. H., and Warren, S.: J. Exper. Med. **35**:187-202 (Feb.) 1922.
53. Murphy, J. B., and Nakahara, W.: J. Exper. Med. **31**:1 (Jan.) 1920.
54. Von Marschalkó, T.: Arch. f. Dermat. u. Syph. **84**:411, 1907.

with leukocytes, new formation and widening of the vessels and the building of a cell infiltrated wall, mainly of plasma cells. To this inflammation soon a connective tissue proliferation enters, which progresses toward the center and walls off the tumor elements. Hand in hand with these inflammatory changes go changes in the tumor cells, a slow shrinking, an inhibition of mitoses, a degeneration and necrosis. I consider these changes secondary to the primary inflammation, and think the leukocytes have a primary rôle in causing degeneration of the cancer cells. The walling-off picture described above would also explain the late recurrence provided insufficient treatment had been given either to make a good barrier or completely inhibit the tumor cells.

SURGERY

Knife incision has one advantage over radiotherapy in that it removes the affected tissue completely in the minimum time, and allows an accurate diagnosis. It is rarely indicated in early or moderately advanced cases but should not be decried as a useful method. There is no necessity for a gland dissection, a local operation with a good margin being sufficient. In some places, a fine linear, scarcely perceptible scar can be obtained, but in others the cosmetic result cannot anywhere nearly approach that of radiation. A decided disadvantage is the danger of local implantation of viable cells, so that "incomplete excision with the knife is more dangerous than a failure from the other methods." [55] In spite of this, Hazen reported a series of Bloodgood's excisions with 86 per cent. permanent cures and, omitting the cases hopeless from the start, 93 per cent.

It is probable that cautery excision has come to the front on account of the danger of spreading the growth by knife dissection. For extensive growths in which radiation therapy has failed, Horsley [56] has devised a technic which consists in cautery destruction of the lesion, cautery dissection and removal, and a plastic repair by rotating a flap from a distance. The latter step Horsley considers especially valuable in that it introduces a new and resistant soil to any attempt at recurrence.

Without doubt a new step in advance has been taken by Clark,[50] in the use of desiccation. This means that there is just sufficient heat used to dry out the growth but not to carbonize the tissues. A high frequency current is employed and an extremely fine steel needle in an insulated holder is applied so as just to brush the lesion. The depth of penetration depends on the time of contact and the power driving the

55. Bloodgood, J. C.: The Surgical Treatment of Cutaneous Malignant Growths, J. A. M. A. **55**:1615-1621 (Nov. 5) 1910.

56. Horsley, J. S.: Surgical Treatment of Extensive Basal Cell Carcinoma, J. A. M. A. **78**:412-416 (Feb. 11) 1922.

current. After the neoplasm is dried out, it is curetted away. Local anesthesia is necessary. The method is especially useful in cancer on the eyelids, inner canthi, and on the conjunctiva, the last named being a type considered by Francis.[57] Clark's results, in eighty-four of these cancers, make a very favorable impression. Wyeth [58] has confirmed and extended Clark's results, and calls the method monopolar endothermy when used for desiccation as above and bipolar endothermy when deeper treatment is necessary. The monopolar current is one of high voltage and low amperage, and the bipolar is the reverse. The only drawback to the method is the expense of the apparatus.

The progressive and up-to-date treatment consists in the use of every form of therapy that has proved its worth. Consequently, the modern hospital should be prepared to render the utmost service by a cooperation between surgeon, dermatologist and radiologist in the consideration of the suitable treatment in each individual case.

Part II

In the previous portion of this paper, the basal cell cancers were discussed. Before passing on to the squamous cell growths, two cases of unusual interest will be considered. It is possible that these cases represent a transitional type between the basal cell and squamous cell cancers. Case 23 would probably be considered, by some authorities, to be a basal cell lesion of the "terebrant" class, an ulceration which causes horrible mutilations by invading the cavities of the face. These terebrant ulcers, according to Darier,[59] are characterized by a slowness of evolution (from ten to thirty years), a tenacity, manifested by recurrence after operation, a localized malignancy, and death by hemorrhages and meningitis.

Unfortunately, no histologic study could be made in this instance. The author considered the foregoing diagnosis to be the logical one till assured by a very competent dermatologist that he had treated the man years previously for lupus erythematosus about the nose and cheeks, and that the ulceration had started in this area. Basal cell cancers do not arise in lupus, the squamous cell type being the rule, according to the reports in the literature. There was absolutely no effect from radium treatment, in this instance.

The second case shows pathologically the structure of both basal and squamous cells. The history of the long duration and the beginning as a subcutaneous nodule suggests a sebaceous cyst origin. Seff and

57. Francis, L. M.: Arch. Ophth. **50**:331 (July) 1921.
58. Wyeth, G. A.: Ann. Surg. **79**:9-10 (Jan.) 1924.
59. Darier, J.: Brit. J. Dermat. & Syph. **34**:145-149 (May) 1922.

Berkowitz [60] have reviewed the literature on epitheliomatous degeneration in sebaceous cysts, and this patient resembles some of the previously reported cases. Ewing [61] shows the photograph of an almost similar case in his "Neoplastic Diseases," but he considers his case a basal cell cancer, and Royster [62] presents an epithelioma and a sebaceous cyst occurring side by side, the malignant portion starting where there was trauma from a comb. The presence of "pearls," in the squamous cancer portion of the growth, would be against the diagnosis or cubocell cancer according to the description given by Hazen.[63] It would quite properly fall into the classification of Darier,[59] carcinoma spinobasocellulare (epithelioma metatypique). He reports eighteen examples which correspond to the mixed type pathologic picture and nine cases that Hazen would call cubocell cancer. The characteristics of these two groups are the ability to invade the glands and generalize; and the resistance to radiation. This group as a whole is not at all common in this country.

SQUAMOUS CELL CANCER, SPINOCELL CANCER, PRICKLE CELL CANCER, EPITHELIOMA (ENGLISH) AND EPIDERMOID CANCER

AGE, SEX AND RACE

Although it is proper to include the cancers of the tongue and mouth, this paper will be limited to the squamous cell growths occurring on the external surface only. This form of cancer of the skin is probably more common than the basal cell due to the frequency of growths on the lower lip. The age of onset is the usual cancer period, the highest incidence being from 45 to 70 years, except for certain forms which arise in lupus vulgaris scars. These lupus cancers occur frequently in young adults, according to Savatard.[9] It is the exception for the other types to be found under 30 years of age, though a certain number of such patients will be recorded in every large series. Thus, in 187 cases of epidermoid cancer of the lip, there were six people under 30 years of age.[64]

Squamous cell cancer is relatively more common in men than in women, owing to the extreme rarity of lip cancer in the latter and the frequency of exposure to hazardous occupations in the former. These points will be more fully considered under etiology.

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60. Seff, I., and Berkowitz, S.: Surg., Gynec. & Obst. **23**:460 (Oct.) 1916.
61. Ewing, J.: Neoplastic Diseases, Ed. 1, Philadelphia, W. B. Saunders Company, p. 814.
62. Royster, H. A.: S. Clin. N. A. **2**:1293 (Oct.) 1922.
63. Hazen, H. H.: Skin Cancer, 1916, p. 82.
64. Simmons, C. C., and Daland, E. M.: Surg., Gynec. & Obst. **35**:766-771 (Dec.) 1922.

There is no racial or other immunity to this type of cancer, the dark races being as frequently involved as any other, in all probability. Statements that certain tribes in inaccessible portions of the world, such as tropical Africa, China, or the Arctic, are free from cancer must carry little weight, for various reasons. The impossibility of getting accurate data, the fact that the average longevity does not bring these races into the cancer age period, and numerous other factors should be evaluated before such a report is made.

ETIOLOGY AND OCCUPATION

Etiology and occupation are often intimately bound up in the causation of squamous cell cancer. For this reason no consideration of the one can be undertaken without bringing in the other.

The essential etiologic agent is not known, according to most writers. Loeb [65] states that we know a great deal about the external factors but very little about the internal, those inherent in the cells.

1. *Injuries.*—Traumas of various kinds, such as the rubbing of a jagged tooth or dental plate, bruises, anything that will cause a repeated injury to the tissues, is liable to localize the carcinoma formation to that area. The tearing off of the mucous membrane by smokers who allow the cigaret paper to stick, the heat and mechanical irritation of a pipe stem, burns and cuts made while shaving are among the contributory causes cited. Chambers [66] reported a squamous cell epithelioma of the hand following a single burn.

2. *Dermatoses.*—Squamous cell cancer of the skin may arise in any of the common dermatoses, such as senile keratoses, warts, seborrheic keratoses, leukoplakia, psoriasis, papillomas and cutaneous horns. One of these conditions is usually the precancerous dermatosis following chemical injury on which occupational cancer grows. Cutaneous horns have been followed by carcinomatous degeneration at the base in 12 per cent. of 109 cases.[21] The psoriasis patches that have become malignant have usually followed a long course of arsenic medication,[67] and acid irritation has started some of the otherwise benign warts on the road to malignancy. The development of cancer on lupus erythematosus is rare. Dubreuilh and Petges [68] reviewed the literature on this subject up to

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65. Loeb, L.: Etiology of Cancer of the Skin, J. A. M. A. **55**:1607-1611 (Nov. 5) 1910.

66. Chambers, T. R.: Ann. Surg. **64**:513 (Nov.) 1916.

67. Hartzell, M. B.: Am. J. M. Sc. **118**:265, 1899. Sutton, J. B.: Brit. M. J. **2**:788 (Dec. 9) 1916. Hamilton, G. R.: Brit. J. Dermat. **33**:15 (Jan.) 1921. Pye-Smith, R. J.: Lancet **1**:1313, 1913.

68. Dubreuilh and Petges: Ann. de dermat. et syph., 1909, pp. 102-106.

1909. Janeway [69] reported a case which he treated in 1910, and Wander [70] made an additional contribution, in 1921, when he added four cases, a percentage of 3.6 per cent. of the 110 cases he had seen.

3. *Scars.*—It has long been known that prickle cell cancers may develop in the scars of burns, injuries, syphilis and tuberculosis. The scar itself represents a past process, there being no activity in any of the lesions. There is an abundant literature on lupus vulgaris scars, roentgen-ray treatment and cancer development, some authors asserting that it is the roentgen ray which is at fault. The cancer may arise at a very early age—13 years,[71] but only after lupus has been present at least ten years and usually twenty years and over.[72] Cancer arising in a burn scar is known as Marjolin's ulcer.

4. *Ulcers.*—Any unhealed ulcer that remains an open sore for a considerable time may become the seat of a cancer. Cracks in the lips which remain chronic are especially suitable soil when proper conditions exist. The varicose ulcer, strangely enough, becomes malignant relatively rarely. Gottheil [73] found ten cases in the literature and added three of his own, and several of the men who discussed his paper said they had seen a few cases. Carcinomatous degeneration in bone sinuses and in fistulas also is of relatively rare occurrence. Blastomycosis almost never gives rise to cancer, though Bloodgood [74] had one case in his series. Association of an active tuberculous ulceration and epithelioma occasionally is noted.[75]

5. *Chemicals.*—It is this group that links up with the occupations and with some of the most recent experimental work. Chemical substances that may lead to conditions favoring carcinomatous degeneration of the skin are tar, pitch, soot, shale oil, paraffin, anilin dyes, arsenic, quicklime, anthracene and tobacco. The whole subject of occupational cancer has been beautifully presented by Ross.[76] He asserts that mechanical injury plays very little rôle but that the chemical injury is responsible. He reports that blast furnace and coal dust are harmless,

69. Janeway, H. H.: J. Cutan. Dis. **28**:3, 140 (March) 1910.

70. Wander, W. G.: Arch. Dermat. & Syph. **3**:22 (Jan.) 1921.

71. Iredell: Brit. J. Dermat. **23**:246-249, 1911.

72. Ashihara: Arch. f. Dermat. u. Syph., 1901, pp. 57, 193. Silberstein: Arch. f. Dermat. u. Syph. **121**:653, 1915. Stümpke, G.: Dermat. Wchnschr. **62**:226, 1916. Zeisler, E. P.: J. Cutan. Dis. **37**:62, 1919. Jauch, F. J.: Lancet **2**:704 (Oct. 1) 1921.

73. Gottheil, W. S.: Cancerous Degeneration in Chronic Leg Ulcer, J. A. M. A. **59**:14 (July 6) 1912.

74. Bloodgood, J. C.: Progr. Med., December, 1907.

75. Maclay, N.: J. Laryngol., Rhinol. & Otol. **32**:253 (Aug.) 1917. Stura, G.: Gior. ital. d. mal. ven. **1**:15, 1921.

76. Ross, H. C.: J. Cancer Res. **3**:321 (Oct.) 1918.

but that gas tar and gas tar pitch and soot give rise to warts which become malignant. He thinks that the anthracene fraction is the active one, the naphthalene and creolin fractions being apparently inert. With shale oil and paraffin there is also danger, and some of the anilin dyes, bismarck brown, paranitranilin red and especially dinitrochlorbenzene give rise to lesions on the skin. Arsenic is quite commonly associated with skin cancer. Ross advances a theory to account for the action of these substances.

The problem of occupational cancer has assumed quite an important position because of the workmen's compensation laws, in most advanced countries. A very thorough investigation has been carried out by the British government following the discovery of a number of cases. O'Donovan [77] gives a review of the literature on cancer in tar workers, and presents twenty-one cases seen in the London Hospital clinic from 1903 to 1920. He mentions the distillation of coal, the handling of pitch by barge hands and railway workers, the making of briquets (patent fuel) as among the hazardous occupations. Bayet and Slosse [78] studied the pigmentation keratoses and cancer in tar workers in France, and noted the striking analogy to chronic arsenic intoxication. They believe arsenic is concerned, as they were able to demonstrate it in the tar, the dust, and in the hair, blood and urine of most of the workers. The cancer which arises in the paraffin and oil workers of the Scottish shale oil industry is reported by Scott.[79] The retort men, oil workers, still men, and laborers also are affected, and he was able to compile sixty-five cases in twenty-two years, nineteen in paraffin workers and the other forty-six in the foregoing laborers. A most interesting group of skin cancers is that which occurs in mule spinners. The growths occur on the left side of the scrotum where there is contact with a bar on the machine. As a consequence there is a constant irritation of the scrotum from the mechanical injury and the mineral oil that coats the faller bar. About three or four cases of this kind are seen every year in the Manchester Royal Infirmary.[80]

Hamilton [81] gives us a report on arsenical keratoses and epitheliomas. Arsenic seems to have a special affinity for the skin and has been demonstrated in the epidermis and hair, according to Hamilton. Wilson pointed out that the keratoses began about the sweat follicles, the drug possibly being eliminated in this manner. Workers who handle

77. O'Donovan, W. J.: Brit. J. Dermat. **32**:215 (July) 1920; ibid. **32**:245 (Aug.-Sept.) 1920.

78. Bayet, A., and Slosse, A.: Compt. rend. Acad. d. sc. **168**:704, 1919.

79. Scott, A.: Brit. M. J. **2**:1108 (Dec.) 1922.

80. Medicine and the Law, Lancet **1**, April 12, 1924.

81. Hamilton (Footnote 67, third reference).

anthracene cake (which contains creosote as well as the anthracene) occasionally develop squamous cell cancer.[82] It is interesting to note that anthracene has the power to absorb ultraviolet light, which may have some bearing. Legge [83] compiled all the pitch, tar and paraffin cancers reported in the British Isles from 1920 to 1922. There were a total of eighty-nine affected, showing that the risk in these occupations is not to be scoffed at. Soot cancer has been recognized for years, especially in England, as the chimney sweeps' cancer of the scrotum. The soot that gives rise to these cancers also contains tars and tar oils with a certain amount of pitch, and, though the sweeps get covered from head to foot with it, the scrotum is practically the only place where the warts and epitheliomas develop.[76] Pichler [84] is very skeptical about the chimney sweeps' cancer and says that, although it seems to be common in England, he has never seen a case himself, although he has examined numbers of sweeps with this condition especially in mind. It may be that the variety of coal burned in the region he has studied accounts for the apparent discrepancy in this soot cancer incidence.

A group of vegetable preparations that probably act through their chemical constituents are tobacco, the betel nut and the charcoal made from decayed vegetable matter burned by the Kangri tribe in India. Tobacco is without doubt partly responsible for the epidermoid growths on the lower lip, as is evidenced by the sex incidence; the sex figures for the rising generation will be watched with great interest.[85] The betel nut cancer is really a cancer of the mucous membrane of the cheek, but will be taken up here because of its bearing on the etiology. Sutton [86] quotes Davis on the preparation of this material, which is chewed by certain tribes of the South Seas and India. Slices of the fruit of the betel palm are dried and wrapped with a pellet of lime and some spices in a leaf of the betel vine. This mixture is called buyo, and when chewed produces a flow of red saliva and blackens the teeth. Cancer occurs where the chewing material is allowed to rest against the cheek, and Davis considers that the lime is the essential cause. Ross [76] says there is tobacco mixed with the betel nut and spices, and that the mixture is kept in a warm place till it putrefies before being used. One of the most remarkable skin cancers is the basket cancer which is found in the natives of the Kangri tribe in Kashmir, northern India. These people carry a basket filled with glowing charcoal under the robes so that it comes in contact with the abdominal wall, or they squat over the basket,

82. O'Donovan, W. J.: Brit. J. Dermat. **33**:291 (Sept.) 1921.
83. Legge, T. M.: Brit. M. J. **2**:1110-1111 (Dec. 9) 1922.
84. Pichler: Zentralb. f. inn. Med. **41**:489 (July 10) 1920.
85. D'Arcy, Power: Brit. J. Surg. **6**:336; 350, 1918-1919.
86. Sutton (Footnote 67, second reference).

allowing it to touch the inner surfaces of the thighs. Cancer arises in these most unusual situations. Ross [76] emphasizes the decaying vegetable matter from which the charcoal is made, but it is difficult to see what rôle this factor can play, if we judge from the illustrations in Woglom's book.[87] The basket but not its contents comes in contact with the skin.

6. *Radiant Energy.*—The early workers in the roentgen rays, especially in the medical field before protection was understood or developed, have almost without exception succumbed to cancer. The sequence has been one or two burns, followed by a dermatitis, keratoses, ulceration, carcinoma and metastasis. Repeated small doses daily have acted on the already damaged skin to bring about the ultimate result. Rowntree [88] has made two contributions on this subject, and remarks that it is a clear-cut experimental production of cancer in man.

With the sad experience of the roentgenologists as a teacher, much more care has been expended on the protection of radium users, although unforseen blood changes have arisen.[89] In spite of these precautions, however, a case of cancer has already been reported.[90]

7. *Experimental Production in Animals.*—The original production of cancers in animals by application of tar to the skin, which was carried out by Ichikawa,[91] has been abundantly confirmed and the results made more striking by Febiger,[92] Leitch [93] and many others. Leitch [93] noted that carcinoma would develop in mice if tar had been applied for a time and then stopped, the initial stimulus apparently being carried to the development of malignancy. The author remarks that it is hard to explain why this occurs if the skin epithelium is constantly being shed and regenerated, as one would expect healthy cells to take the place of the damaged ones. The same experimenter [93] was able to produce paraffin cancer in mice, and succeeded in causing one growth by application of arsenic.[94] Passey [95] had excellent results in the production of soot cancer in his animals, and concluded, from a series of feeding experiments, that the fat soluble vitamin A had nothing to do with it.

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87. Woglom, W. H.: The Study of Experimental Cancer, Columbia University Press, 1913, p. 8.

88. Rowntree, C.: Brit. M. J. **2**:1112 (Dec. 9) 1922.

89. Mottram, J. C.: Brit. M. J. **2**:269 (Aug. 20) 1921.

90. MacNeal, W. J., and Willis, G. S.: Skin Cancer Following Exposure to Radium, J. A. M. A. **80**:466-469 (Feb.) 1923.

91. Ichikawa, K.: J. Cancer Res. **3**:1 (Jan.) 1918.

92. Febiger, J.: Deutsch. med. Wchnschr. **47**:1449-1452 (Dec.) 1921.

93. Leitch, A.: Brit. M. J. **2**:1101; 1104 (Dec. 9) 1922.

94. Leitch, A., and Kennadvay, E. L.: Brit. M. J. **2**:1107 (Dec. 9) 1922.

95. Passey, R. D.: Brit. M. J. **2**:1112 (Dec. 9) 1922.

A fact common to the experimental production of cancer by chemicals, either in human beings or animals, is that there must be a long latent period before malignancy occurs. This has been estimated to be at least ten years in the human being, and the time required in animal experimentation corresponds to a similar relative period in the life span of the animal used. This time element also enters to a large extent in the injury, dermatoses, scars, ulcers and radiant energy groups, though it is at times difficult to establish.

At this point, it seems logical to ask why an internal factor must be assumed to be responsible for the ultimate development of cancer. Is it not fair to predict that any one exposed for the proper length of time to the action of roentgen rays, tar, soot or the kangri basket burn will develop cancer? Perhaps we may ultimately come to recognize three types of response on the part of the body to injury, acute inflammation, chronic inflammation, and when the injury is long and repeated, neoplastic growth.

There is another point of interest in this review of etiologic factors, and that is the type of neoplasm. So far nobody has produced a basal cell cancer experimentally, and the type found invariably in all the other groups above is the squamous cell variety. Experimenters have occasionally produced a sarcoma by the same agents used for the production of cancer.

SEATS OF ELECTION

Squamous cell carcinoma may occur anywhere on the surface of the body. The most common place is at the mucocutaneous border of the lower lip. Frequently, also, there are growths on the face, ears, scalp, extremities, trunk, scrotum and penis. In tar and pitch workers, chimney sweeps and paraffin oil workers (mule spinners), the scrotum is the site of election.[96] In arsenic cancer, two thirds of the cancers are found on the upper and one third on the lower extremities.[81] The face is quite often involved in tar and paraffin workers, the canthi being favorite places in the latter.[83] The hands also are at times affected in both these groups and sometimes the forearms as well. In roentgen-ray cancer, the localization is practically confined to the back of the hands and stops at the coat sleeve level. Occasionally, the face and upper chest show lesions.[88] The kangri basket cancers occur on the skin of the abdominal wall and on the inner surfaces of the thighs. Many chemicals give a multiple distribution of the neoplasm. The localization of all kinds of cancer to the ear has been studied by Broders,[97] who found

96. O'Donovan (Footnote 77). Bayet and Slosse (Footnote 78). Legge (Footnote 83).

97. Broders, A. C.: S. Clin. N. A. **1**:1401 (Oct.) 1921.

62 per cent. squamous cell growths present in his series of sixty-three cases. Cancer of the extremities is very well discussed by Hazen,[98] who found the squamous cell cancer much more common than the other forms, and about equally distributed between the upper and lower extremities. The neoplasms are very rare on the palms.

PATHOLOGY

The two principal varieties of squamous cell cancer are the papillary and deeply infiltrating, ulcerative type. The papillary form rapidly produces a projecting nodule of considerable size which ulcerates early. The ulcer becomes covered with a dry crust, but this is not constantly present, dropping off now and then to be reformed later. The edges of the growth are irregular and indurated and, if the crust is removed, translucent, greyish pink nodules of malignant tissue can be seen. The infiltrating type differs in that there is no external nodule to speak of, simply an abraided looking surface with jagged solid outlines and very extensive deep induration. The bases of these ulcers often look surprisingly innocent. The latter of these two types, nevertheless, is a much more severe neoplasm to handle.

In addition to these more common conditions, there is the so-called malignant wart, which is rare. It differs by the fact that there is no induration and invasion at the base. As a consequence, metastasis does not occur and the growth may be considered relatively benign in character.[99]

All the occupational cancers arise from previously damaged areas of skin. The tar, paraffin, pitch, soot and oil workers have eczema, warts, patches of hyperkeratosis and other patches of atrophy of the skin for years before the malignant ulceration occurs. The warts are often multiple, and it is rare to have malignancy in more than one at a time. The malignant change is shown by the ulceration, the thickened base and the rounded, inverted edge, or by the development of a papule that shows no signs of necrosis within three months.[77]

In roentgen-ray cancer, the most conspicuous changes in the tissues, according to Wolbach,[100] are rarefaction just beneath the epidermis, due to degeneration and imperfect repair; hypertrophy of the epidermis with keratosis and a down growth over the areas of degeneration in the corium, and atrophy or absence of the appendages of the skin. Other writers have found endarteritis, destruction of papillae and connective tissue changes. The scar cancers are often multiple and are easily mis-

98. Hazen, H. H.: Cutaneous Cancer of the Extremities, J. A. M. A. **65**:837 (Sept. 4) 1915.

99. Bloodgood, J. C.: Progr. Med., December, 1904, p. 147.

100. Wolbach, B.: J. M. Res. **21**:331, 1909.

taken for ordinary abrasions and simple ulcerations early in their development.[101] Later, they exhibit the characteristic induration and rolled edge. This form of squamous cell cancer is a very severe one.

The gross pathology, on section, has already been discussed in the first part of the paper under the pathology of basal cell cancer.

Microscopic examination shows masses of large, pink staining, angular cells, either arranged in solid budlike processes, which extend deeply into the subcutaneous tissues, or appearing in whorls of concentric layers, "the onion cells," about central cores of cornified epithelium, the "epithelial pearls." In the early pictures, fine strands of tissue can be made out bridging the gaps between the cells, which fact has led to the names of "prickle cell" or "spinocell." The basal cuboidal cell layer can be made out at times but, in advanced cases, cannot be identified. The prickle cells also tend to lose their identifying spines and coalesce in masses. Hyaline degeneration is observed, in some cells, and very active mitoses, in others. There is often a pronounced round cell infiltration, consisting of various kinds of lymphatic and fixed tissue cells. The more rapid the growth of these squamous cells, the less chance there is for differentiation into the ultimate cornified type. Broders [102] has used this fact in a classification of the malignancy from the pathologic type, and finds a striking clinical verification.

A marked difference between the squamous cell and the basal cell cancer is the ability of the former to produce metastases. The regional lymph nodes should always be carefully examined in every instance in which squamous cell cancer is suspected. This implies a knowledge of the distribution of the lymphatics and the direction of their drainage in order that the examination may be intelligently conducted. How soon may we look for metastasis in these squamous cell cancers? Bloodgood [55] says that, in one of his patients, the epithelioma of the lip was so small that the whole of it could be seen by the low power of the microscope and yet metastases were present in the lymph glands. Hazen [63] states that "cancer may develop in a pipe burn within two months, and a fully developed cancer with metastases to the glands of the neck is possible three months after the initial lesion is noted." Simmons and Daland [64] were unable to palpate the glands in 25 per cent. of their cancer of the lip cases, although microscopically metastases had taken place. The reverse of this picture is given by Mayo,[103] who found palpable glands in a large number of cases of malignancy although the microscopic picture was simple hyperplasia.

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101. Heidingsfeld, M. L.: Skin Cancer, J. A. M. A. **67**:1499 (Nov. 18) 1916.

102. Broders, A. C.: Ann. Surg. **73**:141 (Feb.) 1921.

103. Mayo, W. J.: Significance of Lymphatic Involvement in Infections, J. A. M. A. **80**:221-224 (Jan. 27) 1923.

Figure 27 shows the typical squamous cell microscopic appearance. Photomicrographs are difficult to obtain because of the large amount of reddish staining material.

SYMPTOMS AND COURSE

There are, unfortunately, no symptoms that will send patients to the physician early. The presence and growth of a tumor or ulceration or warty excrescence comprise the only indications of cancer, in the majority of instances. Some of the roentgen-ray ulcerations are extremely sensitive. When enlarged glands are noted by the afflicted person, the disease is usually too far advanced for any therapy.

The growth of these cancers is much more rapid than that of the rodent ulcers, which serves to allow a clinical diagnosis when the situation is suitable for either kind. The great danger of the squamous cell cancer is early metastasis. Some of the epidermoid growths on the lower lip metastasize within a month after they are first noticed. When once metastasis has taken place, the prognosis is much less favorable. There is, of course, a great deal of individual variation depending on the rate of growth, the age, the origin and many other factors. In general, the papillary types tend to be less rapidly progressive than the ulcerative, infiltrating cancers. The malignant warts may be looked on as of local importance only. Some of the industrial cancers also give a good prognosis as metastasis takes place late.[77] The roentgen-ray cancers regularly metastasize after they have become well established, and often there is a mixture of infection and cancer in these lymph glands. Visceral metastasis is very rare but may occur. Late in the course, when there are enlarged masses of metastatic nodules, there is the usual cachexia and anemia seen in other squamous cell cancers.

DIAGNOSIS

In the very early stages, diagnosis is difficult, at times even impossible without microscopic section. This is especially true of the unhealed lesions of the lower lip that we are now seeing within a few weeks from the onset. The only way to know whether these people have cancer or not is to excise the growth and section it. Savatard admits that he cannot diagnose the pin-head sized growths on the skin, but the pea-sized ones of three weeks' duration should be recognized. The tumor is the color of the skin, is raised above the surface and has a translucent appearance, and small blood vessels may be seen coursing over its edge. The center looks fairly hard. Infiltration of the true skin may be present though not always demonstrable. It can be differentiated from a rodent ulcer, which it resembles in appearance, by the rapidity of its growth; a rodent

ulcer takes two years to attain the size of a spinocell cancer of two weeks. The core that differentiates it from molluscum contagiosum cannot be expressed; there are no signs of inflammation, which rules out furuncle; sebaceous cyst also must be dismissed by the examiner.[9] Diagnosis of occupational cancers depends on changes in the appearance of the precancerous lesions, ulceration, induration about the ulcer and hard rolled edges. An ulceration, in a previously healed scar, should be viewed with suspicion, and often the earliest carcinomas in these cases appear as simple papules or keratoses. The well established squamous cell growths are only too easy to diagnose. The difficulty usually encountered is to be certain whether or not metastasis has taken place. Enlarged, hard, shotty glands give the late evidence; the early soft hyperplasia may mask the small nodule.

The differential diagnosis that is most essential to make is between cancer and syphilis. This has already been taken up in the first part of the paper. A point that must be emphasized is that too much time should not be lost in therapeutic test of antisyphilitic drugs. If there is no response within ten days, the lesion should be regarded as malignant.

TREATMENT

The treatment of choice for squamous cell cancer is now, and has been for several years, a battle ground for surgeons and radiotherapists instead of a field for cooperation. This is certainly a misfortune because each group must have something of value that is needed in the war on cancer of this kind. Even when gathered together in a symposium, the antagonism is manifest though the opinions are toned down.

If surgery or radiation were an ideal cure, there would be some basis for the disagreement. As it is, we have no certain relief by any method in a large percentage of cases. For this reason, the educational campaign has been undertaken in the hope that patients may present themselves while there is yet a chance to do something for them.

Let us take cancer of the lip as an example and examine our knowledge as to the proper course of treatment.

SURGERY

Some early lesions of the lip cannot be diagnosed. If malignancy can be diagnosed, metastasis may have occurred. Our methods of examination are not accurate enough to let us be sure on this point. Metastasis as a rule takes place into the submental and submaxillary areas first, and involves the upper cervical and lower cervical glands, superficial and deep, later. There are exceptions to this.

To be successful, the surgeon must remove the original growth with a good margin, and the first barrier glands in the submaxillary and submental triangles in one block. It has been proved, in this form of cancer, that the original growth does not need to be included in this block. If there has been no metastasis, or if the metastasis has been confined to the glands removed, relief is to be expected. When the glands are invaded, on one side, the deep chain on the same side should also be removed, as we cannot be certain that this group is free from disease. Surgical failure is due to too late operation, incomplete operation, careless handling and implantation of cancer cells at the time of operation, or the complications associated with any operative procedure. The primary growth may be removed under local anesthesia and examined by the microscope, thus proving the diagnosis. The gland bearing areas may also be removed, under local anesthesia or nitrous oxid and oxygen. The operation may be done in two stages, in order that infection of the neck be eliminated. The very careful technic advocated by Meyer [104] to insure against wound contamination by viable cells is well worth the attention of surgeons. This danger can, however, be obviated by destruction of the primary lesion by electrocoagulation,[105] which would seem to be an advantage, but it requires an expensive apparatus.

The results from surgery are of course varied. There are many factors to account for differences in statistics, such as age, pathologic picture and time after onset. It is necessary to remove the first lymphatic chain, in every definite cancer case, as it is impossible to tell whether the glands are invaded or free. The danger in local operation only is shown by Bloodgood's [55] figures that, in thirty-two cases, there were only two definite cures, though some went five or six years. Brewer [106] gives the following figures of combined statistics from several hospitals. In Group 1, in which only the primary lesion was removed, 66 per cent. of the patients were well for more than five years. In Group 2, in which the primary lesion and related submaxillary glands were removed, but which were without lymph node involvement, 92 per cent. of the patients were well for more than five years. In Group 3, in which the primary lesion and related submaxillary glands were removed but in which there was positive evidence of lymph node involvement, 34 per cent. were well for more than five years. The lesion from these statistics should be treated by an early and thorough operation.

Simmons and Daland [64] reported 87 per cent. well for more than three years when the glands were not involved, and 28 per cent. well for more than three years when glands were involved.

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104. Meyer, H. W.: S. Clin. N. A. **1**:1643 (Dec.) 1921.
105. Pfahler (Footnote 33). Wyeth (Footnote 58).
106. Brewer, G. E.: Surg., Gynec. & Obst. **36**:169-177 (Feb.) 1923.

RADIOTHERAPY

In order to use radiation intelligently, it is necessary to know in what way the radiant energy affects normal and malignant tissues. The action on basal cell growths has already been taken up, in the previous section. There is almost an unanimous opinion among radiotherapists that squamous cell cancer is much more resistant to radiation than basal cell growths.[107] This should dispose of the theory of selective destructive action on the cancer cells, a theory that has been disproved for animal cancer by Wood and Prime[108] and by Hill, Morton and Witherbee.[109] Damage to the cell nucleus, especially at the time of mitosis, edema of the cell body, vacuole formation in the cytoplasm and vascular changes, endarteritis, are common observations from histologic study of radiated tissue. Injury to the lymphatics and fibrosis of these channels has been assumed to occur, with, so far as I can find, no demonstration of the fact. Murphy[110] and his co-workers think the good results are due to indirect stimulation of general resistance, the action occurring through the agency of the lymphocytes. There is one additional radiation effect that is obtained by inserting bare tubes or "seeds" of radium into the tissues, direct caustic action, a necrosis in a zone about the implanted material.

The rationale of radiotherapy consists in an attempt to damage the primary growth by direct caustic action, by injury to the nuclei of the cells, by promoting a barrier of lymphocytes about the growth, and by shutting off the channels draining from and the blood supply to the area. Any metastatic nodule should be attacked in a similar fashion. The problem for the radiotherapist is to strike a balance that will kill the local growth and its implants and at the same time stimulate the general resistance or at least not reduce it. The difficulty in this program is to know whether the local or the general reaction or both are to be desired; whether, if local, the attack should be concentrated on the malignant cell, or the soil about it, and, if general, where treatment can be given most effectively. There are many other answers yet to be given before the way is all clear.

In well defined cancer of the lip, the prognosis depends on many factors, such as age, rate of growth and pathologic type. Quick[111]

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107. Pfahler (Footnote 33). Quigley (Footnote 46). Morrow and Taussig (Footnote 47).

108. Wood, F. C., and Prime, F.: Lethal Dose of Roentgen Rays for Cancer Cells, J. A. M. A. **74**:308 (Jan.) 1920.

109. Hill, E.; Morton, J. J., and Witherbee, W. D.: J. Exper. Med. **29**:89 (Jan.) 1919.

110. Murphy, J. B.: J. Exper. Med. **33**:429 (April) 1921.

111. Quick, Douglas: J. Radiol. **2**:1 (Dec.) 1921.

takes these facts into consideration and proposes an expectant plan of treatment for the cervical lymph nodes. This necessitates an exceedingly thorough follow-up system, as the dangers are great. The primary lesion is admirably suited for surface radiation, as there are three sides to offer a cross fire treatment. Surface applications of screened radium are used in nearly every case, although "small glass seeds" are at times introduced into the neoplasm under local anesthesia. The glandular areas are radiated either with radium packs or roentgen rays or both. This is done with the idea that the defense in the lymph glands is stimulated and minute metastatic foci destroyed and that metastases are damaged, when glands are already palpable, making operation safer. The patients are watched and examined from time to time and if a gland develops which is clinically malignant, a complete dissection of that side of the neck is done, under local anesthesia, and small doses of radium emanation buried at all suspicious points. If the glandular mass has perforated its capsule and is extensively invading, emanations are buried uniformly throughout the mass which is left in situ.

Pfahler [112] advocates electrocoagulation of the primary lesion, unless it is too extensive, and external radiation by roentgen rays. Metastatic nodules should be dissected out after radiation as described or treated by radium needles inserted into the diseased area.

Numerous other reports adorn the literature asserting that cure was made by the use of radium alone, by the use of roentgen rays alone, or by the combination of both.

Recurrences and well defined metastases have not responded favorably to radiation alone, according to most writers. Quick [111] frankly admits, "by external radiation alone we do not feel we have ever been able to destroy completely fully developed epidermoid carcinoma in the cervical nodes."

The statistics available for radiation of cancer of the lip are too few and too recent to be of value in a comparison with the surgical figures. It is evident, however, that the primary lesion can be destroyed, in practically every instance, if thoroughly treated, and that in the series of cases in which no metastases has occurred permanent relief should be given by such measures. No one can be certain of this group, according to our present methods of examination. When the glands have been invaded, it is possible that early metastases may be destroyed by radiation, and that the lymphoid structures be stimulated. This is only assumption and, unfortunately, it takes years to prove.[55] It is equally possible that further extension from these glands to the more remote glands may take place. When the glands are definitely involved, direct

112. Pfahler, G. E.: Arch. Dermat. & Syph. 6:428. 1922.

exposure of the area must be obtained by surgery in order to be assured of radiation results, external radiation being inefficient.

It is obvious that, in order to get good radiotherapy figures, a number of needless exposures of the glandular areas of the neck must be carried out. This is time consuming, expensive and uncertain.

SUMMARY

From a comparison of the two methods of treatment, it seems certain that a combination of surgery and radiotherapy is desirable, in every case. The primary growth should be rapidly disposed of by electrocoagulation or cautery removal, thus eliminating one dangerous zone as a focus from which metastasis may occur. Radiation by roentgen rays over the lymph gland area might damage any cells already metastasized and allow a safer surgical removal, again by cautery dissection preferably. An ideal method would be to implant radium emanations at the proper points at this operation. Dangerous secondary foci in the glands would thus be removed and the tissues thoroughly treated at the same time by operation. Careful follow-up and postoperative radiation would complete the treatment of choice. It is not possible, in every locality, to have radium emanation or men trained in its use available. Thus, while I do not deny the claims of either side in this controversy, the fact remains that there are more men who have the proper surgical qualifications to carry out the surgical treatment than there are radiotherapists expert or daring enough to undertake the radiation treatment. For that reason alone, until we have more radiotherapists well trained and the method better standardized, the patient in the average community will undoubtedly fare better at the hands of the surgeon. Wherever possible, cooperation between surgeon and radiotherapist will offer the best chance for bettering our results. One additional point, whenever it is possible, malignant tissue should be removed. No matter how well it is killed in situ, the sad experiences of the past indicate that the risk of leaving malignant tissue behind is to be avoided.

Squamous cell cancers of the scalp and forehead do not require removal of the regional glands; cancers of the face, cheek, eyelid, chin and nose, however, should have the glands removed also.[55] Growths on the extremities and scrotum are prone to metastasize and the regional glands are frequently involved. The squamous cell growths on the ear may metastasize to the parotid, preauricular or postauricular glands or to glands of the neck.

REPORT OF CASES

CASE 1.—*History.*—F. B., a man, aged 44, first seen, Feb. 3, 1923, complained that, four or five years before, a small pimple came on the right side of the nose. It scaled over and the scab dropped off, but the base never completely

healed. It grew slowly but steadily in size and bled occasionally, and at times was very itchy.

Examination.—There was an area on the right side of the nose, just above the ala, about 2 by 2.5 cm. in diameter, of which the edges were hard, elevated above the surrounding skin and bluish white. The center was covered by a yellowish dry crust, with a few red granulations in places. There was quite

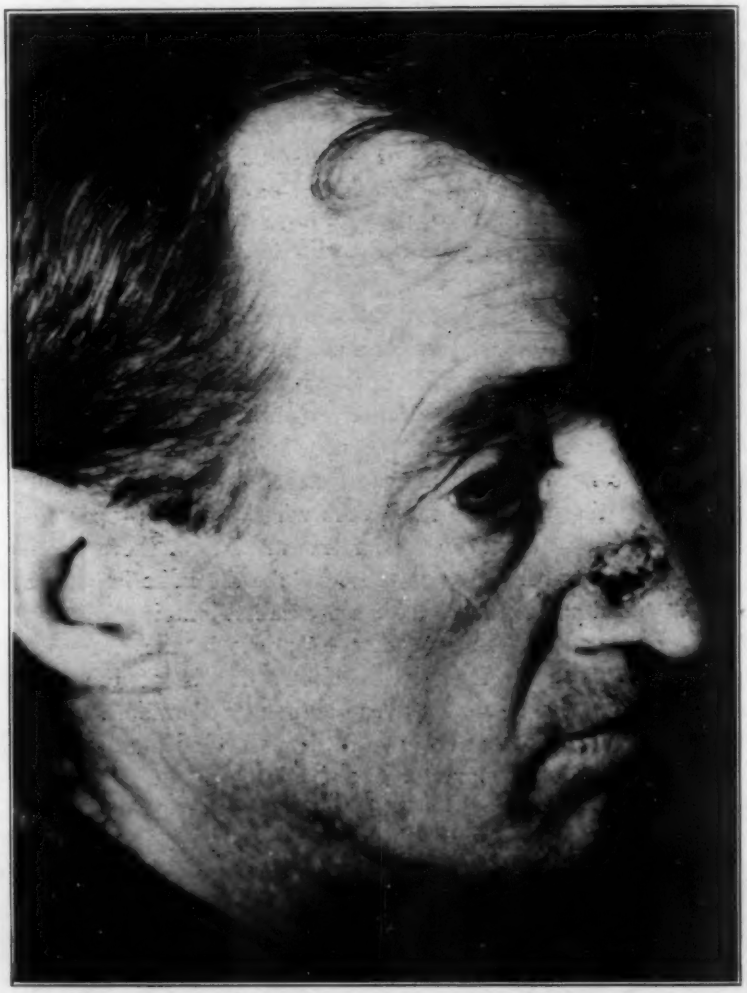

Fig. 1.—Flat basal cell cancer in common situation; edge raised and indurated. Radium caused the growth to disappear.

a deep depression just above the alar cartilage, as though the underlying cartilage were bound in the growth. A slight inflammatory zone was present about the periphery of the sore (Fig. 1).

The Wassermann reaction was negative.

Treatment and Course.—Radium was applied. The growth gradually healed.

CASE 2.—*History.*—J. S., a woman, aged 58, first seen, Aug. 8, 1922, had a sore on the upper lip years before but it had healed. Ten years before, a growth appeared on the left nostril. It was about the size of a pea. It gradually grew larger and bled freely if injured. Six treatments with the Finsen light did not affect the growth in any way.

Examination.—There was an ulcerated area, 2 by 3 cm., with raised edges, occupying the whole alar region of the left side of the nose. The edges were

Fig. 2.—Ulcerated basal cell cancer on ala of nose and multiple senile changes in skin. Roentgen rays caused the growth to heal.

hard and heaped up. There were white, red and yellow spots on the front edge of the lesion. The ulcer extended into the alar cartilage, destroying its mid-portion. There was a serous discharge from the base. There was a healed whitish scar at the right nasolabial junction (Fig. 2).

The Wassermann reaction was negative.

Treatment and Course.—A series of four roentgen-ray treatments were given. The ulcer has been completely healed, since Nov. 21, 1922.

CASE 3.—*History.*—R. L., a man, aged 84, first seen, Dec. 27, 1922, had noticed a small growth in the angle between the right eye and the bridge of the nose three or four years before. It was very small at first, but gradually increased in size. Treatment consisted in various local applications.

Examination.—There was a small superficial ulceration on the right side of the bridge of the nose near the inner angle of the eye. The edges were raised above the surrounding skin and were indurated. The ulcer was covered with a reddish brown crust. It measured 0.5 cm. in diameter (Fig. 3).

The Wassermann reaction was negative.

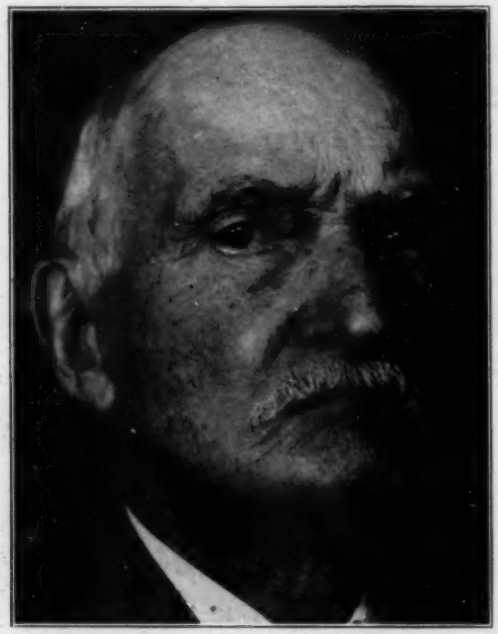

Fig. 3.—The inner canthus is a common site for basal cell cancers. Radium is especially useful in the treatment of these cases.

Treatment and Course.—Radium was applied, from Dec. 27, 1922, to Jan. 17, 1923. The ulcer completely healed.

CASE 4.—*History.*—H. K., a woman, aged 55, first seen, Aug. 9, 1922, said that, about five years before, a little wartlike growth had appeared on the right side of the nose near the inner angle of the eye. It gradually enlarged, ulcerated, and bled easily if injured. Various ointments were used for treatment, with no beneficial result.

Examination.—There was an ulcerated area, 1.5 by 2 cm. in diameter, at the inner canthus of the right eye. The edges were slightly raised, hard and rolled. The base was clean friable granulation tissue. The growth was directly over the tear duct, but the eye was not invaded. No glands were palpable (Fig. 4).

The Wassermann reaction was negative.

Treatment and Course.—Radium was applied August 9, September 19, October 22, January 11 and March 12. Complete healing occurred in February, 1923. The radium was used in March to be absolutely sure that all malignant cells had been killed.

CASE 5.—*History.*—P. M., a woman, aged 44, first seen, Nov. 2, 1921, in 1919 had noticed a small growth at the outer corner of the lower eyelid. It came on "like a blister," and began to grow larger. A physician sent her to

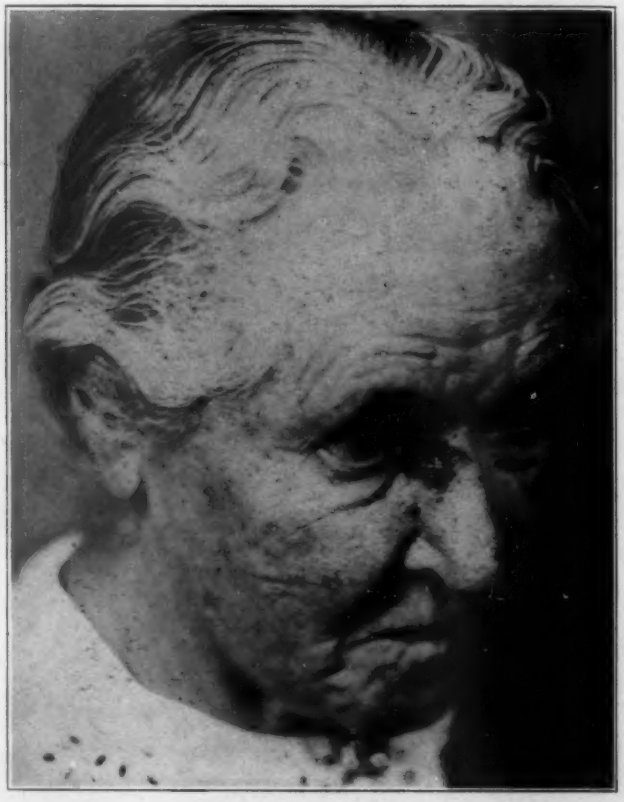

Fig. 4.—Large, ulcerating lesion at inner canthus, with characteristic edge, which was healed by radium treatment.

another city for radium treatment. After two treatments, the growth went away, but it started to come back the following spring (1920). Another radium treatment caused it to heal, and it remained well till the fall of 1921. A small nodule appeared at this time and grew slowly.

Examination.—There was a raised nodule, about 1 cm. in diameter, consisting of what appeared to be normal skin with a hard feel, and two small extensions that radiated into the outer angle of the lower eyelid. The skin over this area was dry and scaly in appearance (Fig. 5).

The Wassermann test was not done.

Treatment and Course.—Radium was applied, Nov. 2, 1920, Dec. 28, 1921, and in February, 1922; also, July 19, 1922, Aug. 10, 1922, and again, Jan. 31, 1923. After the first three treatments, the growth disappeared. It returned, in July, 1922, and was removed by two further treatments. In January, 1923, the patient reported with another recurrence. She was given a heavy dose of radium and should be permanently cured. There was a marked and protracted conjunctivitis following this treatment. The growth disappeared again but, in the spring of 1924, relapsed for the fourth time. Surgical excision was advised.

Fig. 5.—Basal cell growth at outer canthus, which recurred after radium treatment. The depilation of the lower eyelashes should be noted. The importance of a close follow-up is indicated by this case.

Case 6.—*History.*—J. S., a man, aged 44, first seen, May 29, 1922, said that, six years before, a small pimple had come on the middle portion of the right lower eyelid. It became infected and was lanced in New York City. There had been a discharging sore on the lower lid since. He had had six roentgen-ray treatments, one year before, with no result.

Examination.—There was a grayish white, elevated, papillary growth, 0.2 by 0.9 cm. in diameter, on the lower right eyelid at the lid margin. The tissue was firm, not sensitive, and did not bleed easily. There was a thin, threadlike, purulent discharge that contained many cocci on microscopic

examination. The eyelashes were gone in the neighborhood of the growth. There were no enlarged glands made out (Fig. 6).

The Wassermann reaction was negative.

Treatment and Course.—Radium was applied, June 29 and July 17. The growth went away, exposing a meibomian cyst. This was incised by the ophthalmologic service.

The growth recurred in January, 1923. Radium treatment, January 12, caused disappearance of the growth. The ducts of the meibomian glands

Fig. 6.—Small growth on lower eyelid, not a common seat of origin. The growth recurred after radium and was finally excised with excellent results.

were clearly visible after the growth had gone. The question of excision of this infected area was discussed. There was another recurrence in October, 1923, followed by surgical excision and plastic repair. There is no evidence of the growth and an excellent cosmetic result, July, 1924.

CASE 7.—*History.*—J. F., a man, aged 52, first seen, Jan. 14, 1922, stated that, about two months before, he had noticed a growth on the left side of the temple. It had a dry scab over it, which came off when he washed his face, leaving a bleeding base. It remained about the same size.

Examination.—There was a small, elevated, hard, noninflammatory lesion of the left temple. The surface was abraded, and the base bled slightly and oozed serum. The growth measured 0.5 cm. in diameter (Fig. 7).

Treatment and Course.—Radium was applied, Jan. 14, 1922. The growth disappeared in one month, and had not recurred in July, 1924.

Case 8.—*History.*—F. C., a man, aged 49, first seen, Feb. 6, 1922, had had psoriasis on the arms, knees and chest for years; also, a scaly, dry, irritative lesion of the scalp (seborrhea). Twelve years before, he noticed a small

Fig. 7.—Very early basal cell cancer, nodular type, before ulceration had occurred. The cancer disappeared under radium treatment.

abraded area where the bow of his glasses rubbed. This area gradually increased in size. It itched a great deal and caused him to pick at it, after which it bled freely. He treated it with salves and tincture of iodin.

Examination.—There was an area over the right temple about the size of a silver dollar. The center was covered with smooth skin but all about the periphery was a hard, raised whitish blue rim of tissue partly covered with heaped up skin; it was not attached to the underlying tissues, and there were no signs of inflammation or palpable glands in the neighborhood (Fig. 8).

The Wassermann reaction was negative.

A specimen removed for microscopic examination was reported as basal cell cancer.

Treatment and Course.—Radium was applied, February 6, and later until the whole periphery had been covered. The bow of the glasses was altered so that no rubbing occurred in the temporal region. There was complete healing, July, 1924.

CASE 9.—*History.*—C. J., a man, aged 57, first seen, Sept. 27, 1921, stated that his left ear had been badly torn in an accident several years before. In 1919, he noticed a small sore behind the left ear. It ulcerated, and he

Fig. 8.—Very unusual type of basal cell cancer, the annular or "morphea-like." The growth came where the bow of the glasses rubbed, and healed under radium treatment.

came to the New Haven Hospital dispensary, where the ulcer was excised and the skin sewed up. In 1920, it again ulcerated and healed after treatment. In the summer of 1921, it opened again and commenced to discharge. There was no pain associated with this sore at any time.

Examination.—There was a triangular-shaped ulceration behind the left ear. The edge was sharp and deeply undermined. There was an area of scar tissue in the middle, which made it appear as if there were two distinct ulcers. The base of these ulcers was covered with a grayish white mass of débris. There were no enlarged glands (Fig. 9).

A specimen was removed for microscopic examination. It showed basal cell cancer.

Treatment and Course.—Radium was applied several times, with healing. The area involved shows a tendency to break down. It has ulcerated several times but heals promptly under radium.

CASE 10.—J. S., a man, aged 77, first seen, Nov. 10, 1922, came to the New Haven Hospital dispensary for weakness and cough. Examination showed pulmonary tuberculosis. For several years (the exact number not recalled), he had had a growth behind the left ear. He wore glasses the bows of which curved in back of the ear directly to the growth.

Examination.—There was an ulceration, 3 cm. long by 1 cm. wide, behind the left ear. The base of this ulcer was slightly moist and brownish red.

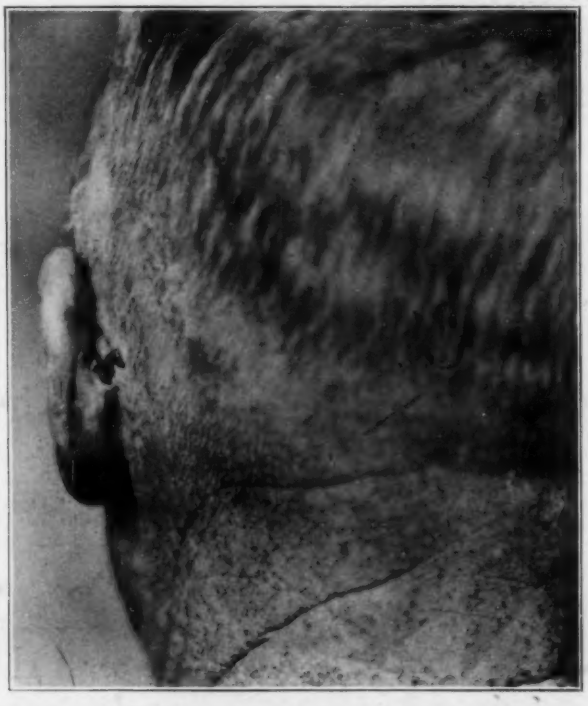

Fig. 9.—Ulcerating basal cell cancer, which healed under radium but did not remain well.

The ulcer looked very inactive. The skin was elevated from 0.3 cm. to 0.4 cm. all about the edges, in a smooth, irregular, firm ridge. A portion of this edge extended on the pinna (Fig. 10).

The Wassermann reaction was not tested.

A specimen was removed for microscopic examination. It showed blue staining cells in whorls, with an almost alveolar arrangement in places. The picture might be that of a sweat gland tumor, although this could not be proved except by serial sections that demonstrated such an origin.

Treatment and Course.—The glasses were altered. Several radium treatments were given. Complete healing resulted.

CASE 11.—*History.*—C. M., a man, aged 62, first seen, Jan. 11, 1923, twelve years before had a scratch on the right ear. It scabbed over with a thin

scab that occasionally fell off only to reappear later. It never permanently healed and grew slowly in size.

Examination.—There was an oval lesion, about 1 cm. in diameter, on the middle portion of the scapha. It was elevated about 0.3 cm. above the surrounding skin. Its edges were hard and bluish white. The center was ulcerated and red. No enlarged glands were palpated (Fig. 11).

The Wassermann reaction was negative.

Treatment and Course.—Radium was applied. The result has been favorable as far as treatment has gone. No lesion was visible, July, 1924.

Fig. 10.—Ulceration with hard, raised edges behind the ear, arising in an area of irritation from eyeglasses, diagnosed as basal cell cancer.

CASE 12.—*History.*—V. H., a man, aged 73, first seen in July, 1922, twelve years before had been kicked in the right side of the face by a horse. He had already had a wartlike sore that had been in that area for several years. Following the horse kick, the sore began to grow and increased in size steadily during the spring. He has always had a crawling sensation in this region.

Examination.—There was an ulcerated growth on the right cheek with hard, heaped up edges and a crusted hemorrhagic base. The area measured 2 by 3 cm. in diameter. There was a linear scar extending lateralward from the growth (horse kick) and considerable induration in the tissues surrounding the lesion. No palpable glands were made out.

There were many patches of senile change in the skin, greasy, brownish seborrheic warts (Fig. 12).

Treatment and Course.—Radium was used in two applications. There was complete healing within two months.

CASE 13.[113]—*History.*—S. A., a man, aged 24, first seen, Feb. 15, 1922, for eight months and possibly longer had noticed a small sore on the forehead just to the left of the median line, about half way between and above the level of the eyebrows. It started as an abrasion, scabbed over, but never completely healed. It increased in size slowly.

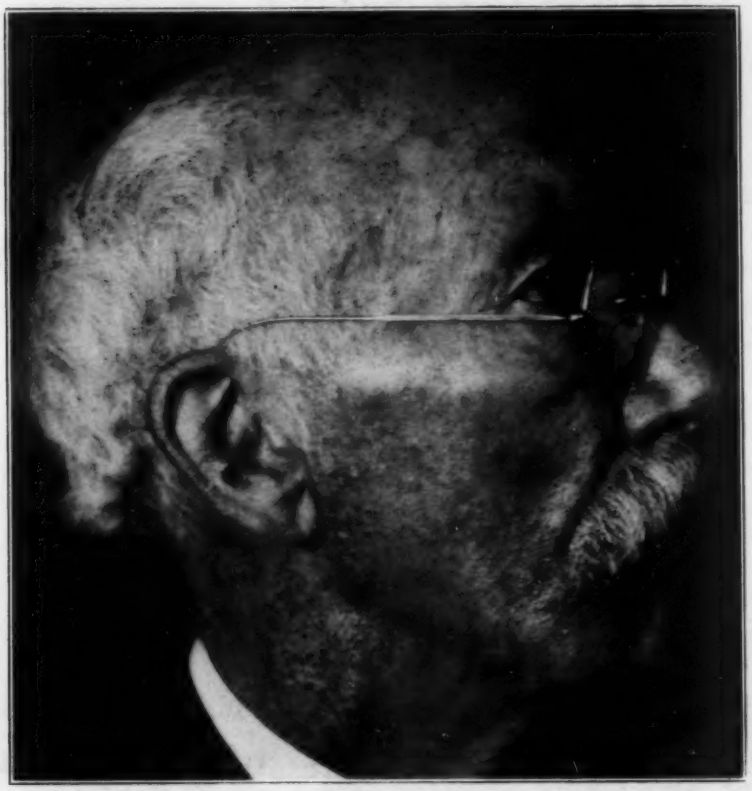

Fig. 11.—Characteristic basal cell cancer in an unusual situation.

Examination.—There was a small ulcer, 1 cm. long by 0.5 cm. wide, with a reddish, granulating center and slightly elevated edges. These edges were moderately firm but not distinctly hard. There was no induration in the surrounding skin (Fig. 13).

The Wassermann reaction was negative.

Treatment and Course.—Excision of the ulcer was done under procain anesthesia. Closure was made. The surrounding skin was treated by roentgen ray. There is a scarcely perceptible linear scar, and no recurrence has taken place. Diagnosis, on microscopic examination, was basal cell cancer.

113. I am indebted to Dr. John Lane of New Haven, Conn., for the privilege of reporting this case.

CASE 14.—*History.*—T. B., a man, aged 78, first seen, April 14, 1922, had broken his nose by firing a shotgun when a boy. There was a scar there which several years before (exact date not recalled) scabbed over. The scab came away several times and the sore almost healed, but never completely. Finally, a growth came and slowly increased in size. A second lesion also appeared on the nose and grew steadily.

Examination.—There were two areas involved. The first of these consisted of a hard, bluish white, umbilicated nodule, measuring 1.5 cm. in diameter

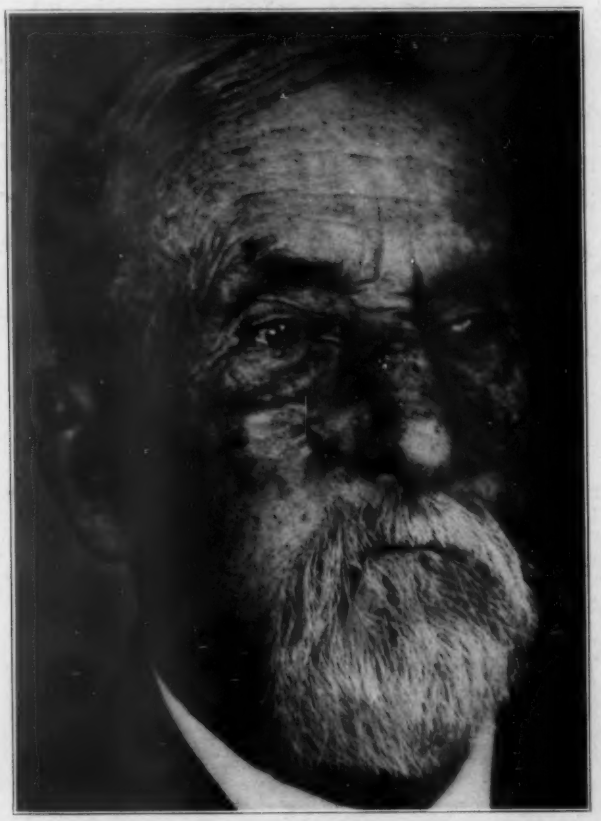

Fig. 12.—Basal cell cancer of face arising in a patch of skin change that followed a horse kick.

and elevated above the surrounding skin 0.5 cm. The skin over it was intact. It was roughly circular in outline, situated on the left side of the apex of the nose, with a small finger-like extension running toward the inner canthus.

The second lesion occurred about 2 cm. above the tip of the nose on the left side. It was circular in outline, raised above the skin level, and measured 2 cm. in diameter. It was definitely ulcerated. The base of the ulcer was covered with a reddish brown crust and exuded serum. The edges were hard and elevated (Fig. 14).

The Wassermann reaction was negative.

Treatment and Course.—Two radium applications were made. The growth entirely healed, with pliant, circular scars.

CASE 15.—*History.*—J. M., a man, aged 60, first seen, April 3, 1922, had had a sore on the right cheek eighteen years before. It was burned out by a surgeon. Another sore appeared on the nose at a later date, and was treated in a similar way. Three years before, a third sore came on the right side of the nose. It was treated by roentgen ray several times without change in its size or character.

Fig. 13.—Basal cell cancer occasionally arises in a young person. Excision gave a good result in this instance.

Examination.—There was a scar on the right cheek at the outer edge of the nasolabial fold. It was soft and scarcely visible. It represented the first growth. There was a second scar on the right side of the nose just above the alar fold, with a small, yellowish white nodular recurrence in its center. This was the second growth. A third more recent and more active lesion was situated at the nasofacial junction above the ala. It was raised about 0.5 cm. above the rest of the skin; the edges were hard and rolled, and there was considerable induration about it. It was ulcerated, and the base of the ulcer was covered by a dry, reddish scab. It measured 1 cm. in diameter. There were several small, pinkish nodules extending in a ridge toward the

inner canthus. There was a patch of scaly keratosis near the outer canthus (Fig. 15).

The Wassermann reaction was negative.

Treatment and Course.—Radium was used three times. The growths healed within two months. During the following year, two new nodules developed, one in the skin below the right lower eyelid and a second over the bridge of the nose. These growths responded easily to radium treatment.

CASE 16.—*History.*—B. G., a woman, aged 67, first seen, Oct. 6, 1921, had had a growth on the left temple for more than twenty years. It came on as a small red area where her glasses rubbed and slowly spread. Five or six

Fig. 14.—Basal cell growths are often multiple. This patient shows both a nodular and an ulcerated cancer, and radium gave a very good result.

years before, a small wart came back of the right ear. It was covered with scabs and scales and gradually increased in size. Two and a half years before, a small wart with a black scaly top appeared on the left side of the chin. These scales were easily brushed off, in washing the face, and a bleeding ulcer was left. This ulcer began to enlarge.

Examination.—In the left temporal region anterior to the left ear there was a round, crater-like, nodular lesion, measuring 2 cm. in diameter. It was in the form of a slightly raised ring and was rather hard. The skin

in the center was red and, in one area, was ulcerated and infected. Just below and behind the right ear was a second almost similar growth. The third was situated over the mandible on the left side and consisted of a hard, raised, infected ulcer somewhat larger than the other two lesions. There were many evidences of senile change in the skin, keratoses, seborrheic warts and atrophy (Fig. 16).

The Wassermann reaction was negative.

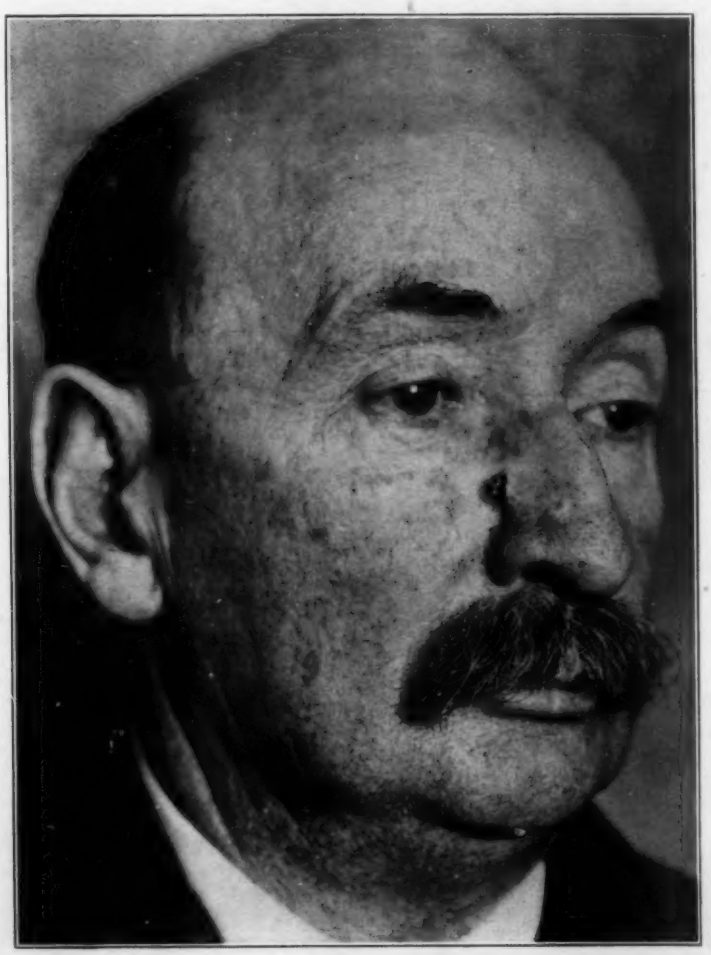

Fig. 15.—Another example of multiple lesions, all basal cells. Cautery cured one growth, and radium removed the others. During two years' observation, two further growths developed in new locations.

A specimen excised for microscopic examination showed typical basal cell cancer.

Treatment and Course.—Several radium applications were given. The growths were healed in July, 1924.

CASE 17.—*History.*—B. L., a man, aged 82, first seen, Dec. 5, 1921, ten years before had noticed a growth on the very tip of the nose. It looked like a

boil but did not break down for a long time and, after this happened, it would not heal. It was finally cauterized with trichloracetic acid and scarred over. It remained closed for about two years, but there was always a feeling of irritation present. It next ulcerated just to the right of the previous growth and has never entirely healed since, although much benefited by treatments. It kept on spreading along the right side of the nose. Another ulceration appeared on the left side. After radium treatment in another city,

Fig. 16.—Multiple basal cell cancers. The growth on the left side of the chin is in an unusual place for basal cell cancer; a third lesion was present behind the right ear. These were removed by radium.

in June, 1921, there were only two pin-head sized ulcers unhealed, but these slowly enlarged again. In September, 1921, the patient had further radium treatment with an almost identical result. In December, 1921, he had a series of six roentgen-ray treatments, which caused healing of the main ulcer but did not affect the rest of the growth.

Examination.—The right nostril was eroded away, about 1 cm. in its anterior portion and about 0.5 cm. at the posterior edge. There was also an ulcer on the surface of the right ala, measuring 0.5 cm. in diameter. The

whole tip of the nose appeared to be covered with very thin, almost translucent atrophic skin. The edges of the main ulcerated areas were not raised but consisted of deep red granulations. There was invasion of the septal and alar cartilages and involvement of the mucous membrane of the right nostril. The small ulcer on the ala had raised indurated edges and a base covered with a yellow crust (Fig. 17).

The Wassermann reaction was not tested.

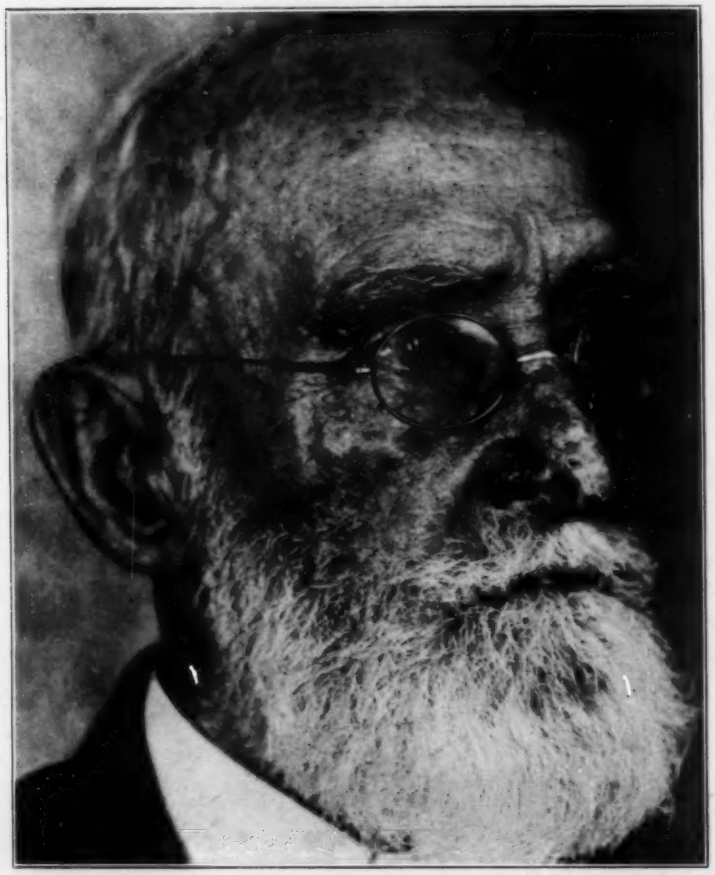

Fig. 17.—The rodent ulcer tendency is very well shown in this patient. When the cartilage becomes involved, the lesion is very difficult to heal.

Treatment and Course.—Two radium treatments were given. There was marked improvement. When last seen, almost complete healing had taken place. It is doubtful whether the area will remain well.

CASE 18.—*History.*—D. M., a man, aged 72, first seen, April 3, 1922, fifteen years before had had a severe eczema over the entire body. He recovered from this, except for a small area extending over both sides of the end of the nose. The itching and scabbing over these points have remained practically the same since the onset, although improved at times. Two and one-half years before, the lesions were healed by four roentgen-ray treatments.

He did not follow instructions to report for further observation, and two months later the itching returned. The condition has steadily progressed since that time.

Examination.—There was an erosion of both alae and the tip of the nose, as if there had been an amputation of these structures. The septum also was deeply involved. The lesions were covered with a dark reddish brown crust, in which there were small pin-point areas oozing serum. There was slight induration about the ulceration and a zone of marked inflammatory reaction (Fig. 18).

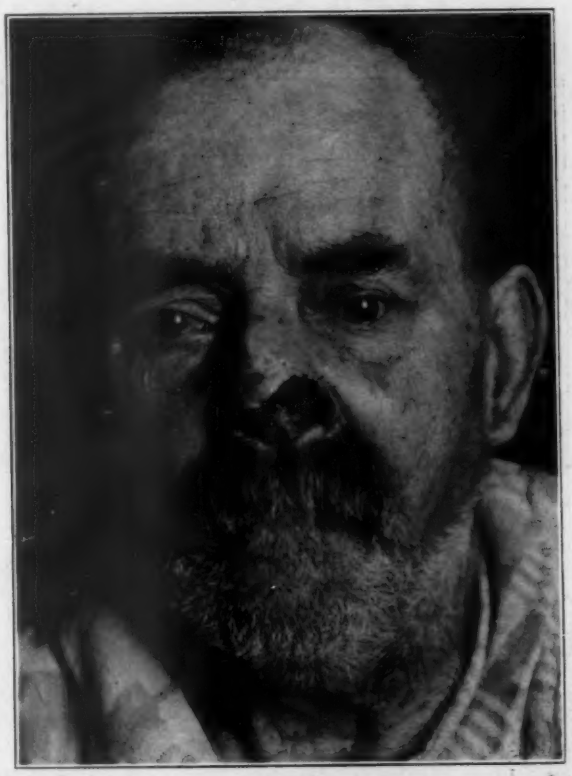

Fig. 18.—A real rodent ulcer arising in a patch of eczema and extending without regard for structure.

The Wassermann reaction was negative.

Treatment and Course.—Radium was applied three times. The patient then discontinued further treatment. Cauterization was refused. No effect was noted.

CASE 19.—*History.*—M. R., a woman, aged 67, admitted to the hospital, Feb. 19, 1924, stated that, about twenty years before, a small pimple had come on the nose near the inner angle of the left eye. For the following fifteen years, the little sore remained about the same, never causing any pain or discomfort. Some four or five years before, the growth began to enlarge and continued to extend over the left upper and lower eyelids as an angry sore. She had had no pain but wished to be rid of the condition because of its ugly appearance.

Examination.—The whole upper eyelid was replaced by a mass of cancerous tissue and in part destroyed, leaving a notch through which the globe appeared to be uninvolved. The lower lid was similarly invaded by nodules of malignant tissue. There was a marked conjunctivitis present. The bridge of the nose on the left side and a scarlike extension along the nasofacial fold were further portions of the growth. A series of small nodules surrounded the scarred area (Fig. 19).

Treatment and Course.—Radium was applied on several occasions, with almost complete disappearance of the cancer. A small portion left over was excised, and the diagnosis of basal cell cancer was confirmed. A corneal ulcer followed the clearing up of the growth, owing to the fact that there was no

Fig. 19.—Extensive basal cell growth involving both upper and lower eyelids and side of nose. There was marked improvement under radium, but a plastic operation was necessary to cover the exposed eyeball.

eyelid to cover the eyeball and keep out irritating material. A plastic operation was necessary to remedy this defect. Sufficient time has not elapsed to draw any conclusions.

Case 20.—*History.*—C. T., a man, aged 70, first seen, April 4, 1922, for several years (exact time not known) had had a small growth on the right ear, anterior surface, just inside the overhanging edge of the helix, near its topmost point. This tumor has never given any trouble and has progressed only very slowly. For two months, he had had a second nodule on the tip of the nose. This was treated by acids, and there had been a rapid enlargement during the last two weeks.

Examination.—There was an elevated, hard, bluish white nodule on the right ear, in the situation previously described. The center of the lesion was

covered by a scaly, reddish white scab. The appearance was typical for a basal cell cancer. On the tip of the nose, there was a hard, raised, yellowish white, irregular mass, 1.6 by 1.3 cm. The central portion was covered by a brown scab, and the surrounding skin was reddened and full of small, dilated vessels. A biopsy was performed, and the section showed squamous cell cancer with numerous well developed epithelial pearls (Fig. 20).

Treatment and Course.—The lesion on the ear disappeared under radium applications. The lesion on the nose was excised and the raw surface skin grafted. There had been no recurrence, July, 1924.

Fig. 20.—Unusual case of basal cell growth of right ear and squamous cell cancer of nose. The diagnosis could be made, in this instance, by the comparative growth rates.

CASE 21.—*History.*—E. B., a woman, aged 69, first seen, July 6, 1924, stated that, about one year before, a dog had bitten her on the nose. The wound had slowly but steadily enlarged, and was now somewhat tender on examination but not painful otherwise. She had had shooting pains in the legs and bladder trouble, which consisted in frequency, nocturia and, at times, incontinence. She had had one living child by her first husband, and a long series of miscarriages following this normal birth.

Examination.—The patient was a small, thin, highly nervous woman of poor memory. The pupils reacted to light and in accommodation. The heart

was enlarged, with a systolic murmur at the apex; the vessels were sclerosed. The reflexes were normal; no Romberg sign was present. There were scars of old lesions on the skin of the arms and forehead. Over the right side of the nose, extending from the midline to the nasolabial fold, was a deep, punched out ulceration about the size of a quarter. The edges were clean cut and somewhat indurated, but there was no rolling or heaping up. The base of the ulcer was covered by a slough. The surrounding skin was decidedly inflamed. Near the inner angle of the left eye, there was a similar but smaller ulcer (Fig. 21) which was diagnosed as syphilitic ulceration. The blood Wassermann reaction was 4 plus.

Fig. 21.—Tertiary syphilitic ulcer which resembles basal cell cancer.

Treatment and Course.—On potassium iodid, there was a very definite improvement in less than a week. The patient was transferred to the syphilis clinic for further treatment.

Case 22.—*History.*—H. B., a man, aged 70, first seen, April 18, 1922, stated that, something over fifteen years before, he had noticed a small pimple on of the right side of the tip of the nose. This came in a patch of skin disease, considered by a competent dermatologist to be lupus erythematosus. The sore gradually extended, eating away both sides of the nose, more so on the right, where it slowly melted the tissues toward the eye. The nasal septum was bared and in part destroyed; the upper lip was gnawed through to the gum, and the process extended into this also.

Examination.—The whole right side of the nose was missing up to the nasal bone, and the ulceration stopped just short of the right inner canthus. The bridge of the nose remained intact and was covered by normal looking skin. There was a portion of the left upper side of the nose still not involved. This was represented by about 2.5 cm. of tissue. The septum that remained extended from its maxillary attachment in a straight line to the nasal bone. All the cartilage anterior to this line was gone. The inferior turbinates also were eaten away, and there was destruction of the middle portion of

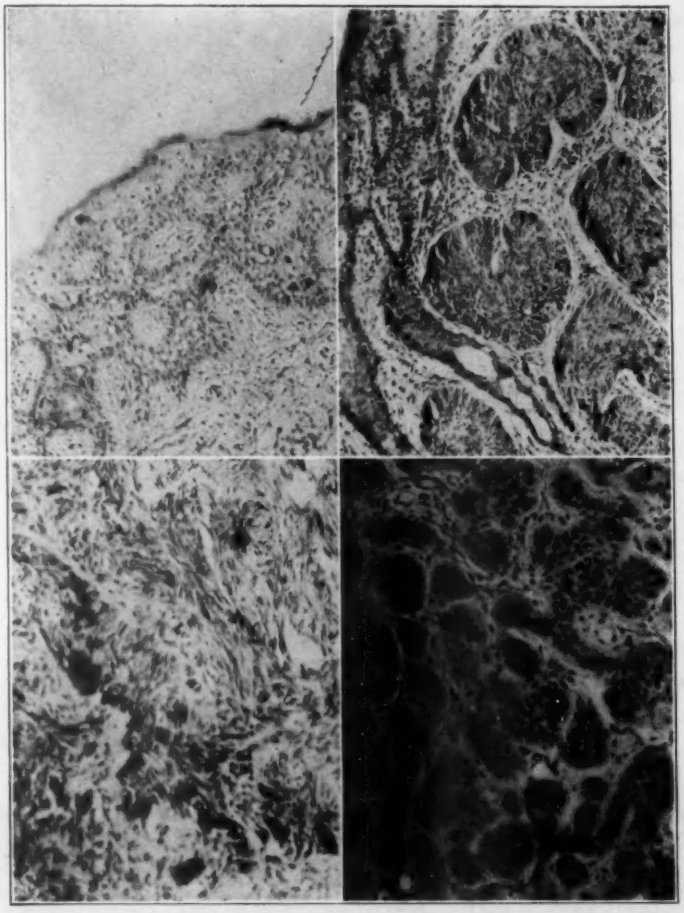

Fig. 22.—Types of basal cell cancer.

the superior maxilla, especially on the right. The whole inner portion of the upper lip, an area of about 4 cm., was eroded. The edges of the extensive ulcer were rolled, hard, nodular and covered by a brownish red crust. The surrounding skin was inflammatory, with numerous small distended vessels radiating toward the growth. There was a mucopurulent discharge in the depths of the wound (Fig. 23).

The Wassermann reaction was negative.

Treatment and Course.—Radium was used in an attempt to control the progress toward the eye and the sinuses. A prosthesis was made to conceal

the mutilated appearance. Cautery excision was advised but refused. Perhaps there has been a checking of the rate of growth, but this is doubtful.

CASE 23.[114]—*History.*—M. J., a woman, aged 53, admitted to the hospital, Feb. 10, 1920, said that she had noticed a small lump, about the size of a bean, in the scalp of the back of the head ten years before (1910). This lump steadily grew in size till it was nearly as large as an orange. It then ulcerated and remained an open sore.

Examination.—On the posterior surface of the scalp covering the occipital region, there was an extensive area of ulceration, 15 cm. long by 10 cm. wide. It extended from the occipital protuberance posteriorly to a point anteriorly

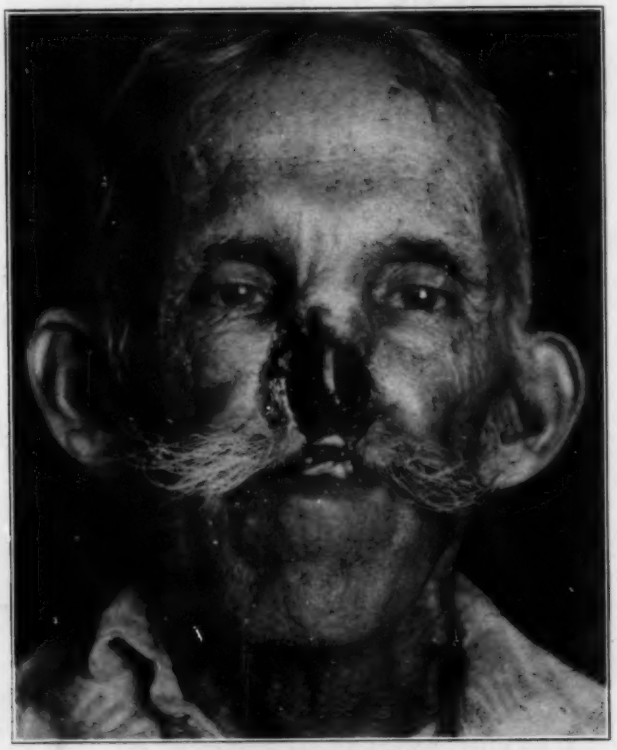

Fig. 23.—Growth that arose in a patch of lupus erythematosus. No microscopic study could be made, but it is either a squamous cell cancer or the "terebrante type" of basal cell.

that might be marked by a line drawn around the calvarium at the level of the back of the ears. The edges of the ulcer were irregular, firm in consistency, and apparently adherent to the skull beneath. The lower portion of the edge on the left side was raised into an irregular excrescence. The base of the ulcer was of an uneven surface covered with granulation tissue, which was bathed in purulent discharge. The upper portion of the neck below the ulcer was swollen and edematous. Discrete lymph glands were not palpable.

114. I am indebted to Dr. N. A. Ludington of New Haven, Conn., for permission to publish this case.

Small, firm, shotty glands were palpable in the posterior triangle on the left side and in the submaxillary region.

A specimen was removed for microscopic examination. It showed characteristic basal cell cancer, with areas of tendency toward squamous cell type. The latter areas were characterized by groups of pink staining cells and a few definite epithelial pearls. There was also considerably more mitotic division than is usually seen in basal cell growths. There was a fairly dense fibrous tissue reaction about the epithelial masses.

The patient was discharged, March 3, 1920. She was readmitted to the hospital, Oct. 1, 1921. Since 1920, she had had numerous roentgen-ray treatments. She came to the hospital this time because of an infection of the ulcerated area. She also had pains in the frontal region and some failing vision. Examination showed the base of the ulcer bathed in a thick, yellow,

Fig. 24.—Extensive ulceration of the scalp; microscopic section showed both basal and squamous cell characteristics.

foul smelling pus. When this was wiped away, two or three areas of denuded, roughened bone from 1 to 2 cm. in diameter were exposed. Almost in the center of the base of the ulcer there was an area, about 2.5 cm. in diameter, in which the process had eaten its way through the tables of the skull, leaving the thickened dura exposed (Fig. 24).

The Wassermann reaction was negative. A culture of the wound grew *Bacillus diphtheriae*. Roentgen-ray examination of the skull showed a destructive process of the upper part of the occipital bone, mainly involving the outer table. She was given 10,000 units of diptheria antitoxin.

Oct. 14, 1921, the wound was much improved. The patient was discharged from the hospital.

Operation and Course.—She was admitted the third time, Nov. 1, 1921, and, November 5, excision of the tumor tissue with underlying bone was done. The epitheliomatous area was outlined, and the incision carried to the bone. The skull was then perforated by a series of burr holes that were connected

by the Montenovesi forceps and the whole mass of bone with attached scalp removed en bloc. The dura was not infiltrated by the growth.

The patient suffered a great deal of pain after the operation and was delirious at times. She improved gradually and was discharged, Dec. 6, 1921.

Feb. 28, 1922, shortly after leaving the hospital the patient had a "fainting attack" lasting several days. She then continued about the same till a few days before admission. At this time, she became quite violent and suffered from pain in the left side, even the pressure of the bed clothes causing attacks. She was irrational for the two or three days preceding this admission.

March 12, the patient was violent, requiring large amounts of sedatives. March 14, she had convulsions all morning, up till 3 p. m., when she became quite cyanotic and weak. She died at 11:15 p. m.

Fig. 25.—Typical squamous cell cancer of lip, the most common situation for squamous cell cancer of the skin.

CASE 24.—*History.*—L. S., a man, aged 42, admitted to the hospital, March 7, 1923, stated that about eight months before he had noted a small pimple about the size of the head of a match near the right corner of the lower lip. It caused no trouble at first but, in a few months, commenced to enlarge. The growth was slow at the beginning but, more recently, has speeded up. The surface was covered by a crust which dried over but did not heal. The sore bled slightly, and the patient applied various medicines on the advice of friends. He smoked a great deal, frequently smoking a clay pipe which he held in the right side of his mouth. He was seen on the street by a medical student and urged to come into the hospital.

Examination.—There was a large ulcerated growth on the right side of the lower lip near the angle. It extended into the mucous membrane of the lower lip and cheek. It was irregularly ovoid in shape and measured 2.5 by 3 cm. in diameter. The edges of the sore were hard and rolled up and the indurated portion extended into the mucous membrane though not very far. The surface of the tumor was covered by a thin crust of cracked dry scabs, except for some raw looking areas. The glands of the submental and submaxillary regions on both sides were palpable as small firm nodules. The deep cervical glands were not palpable. The teeth were in bad condition and somewhat irregular, although there were no sharp snags near the site of the neoplasm (Fig. 25).

Fig. 26.—Cancer diagnosed as squamous cell on account of the rapid growth; a basal cell cancer would require years to reach this size.

The Wassermann reaction was negative.

Treatment and Course.—March 7, 1923, the regional glands of the neck on both sides were treated by roentgen ray.

March 10, radical removal of the submental and submaxillary glands en bloc under nitrous oxid-oxygen anesthesia was done. Immediate frozen section of glands and, later, a careful examination of the whole group was made. There was no metastasis.

March 19, the cancer of the lip was removed, and plastic closure was made, under procain.

March 27, both sides of the neck were treated by roentgen ray. The pathologic report was very active squamous cell cancer, with scarcely any differentiation of the cells.

The patient remained under observation for a year without any signs of recurrence. He had one or two roentgen-ray treatments during this time. Suddenly, within a week, large masses of glands appeared in the deep cervical chains on both sides. The progress was very rapid in spite of irradiation with radium and roentgen ray, and death followed.

Case 25.—*History.*—A. P., a man, aged 61, first seen, March 15, 1922, stated that a growth had started in the temporal region two years before. It was

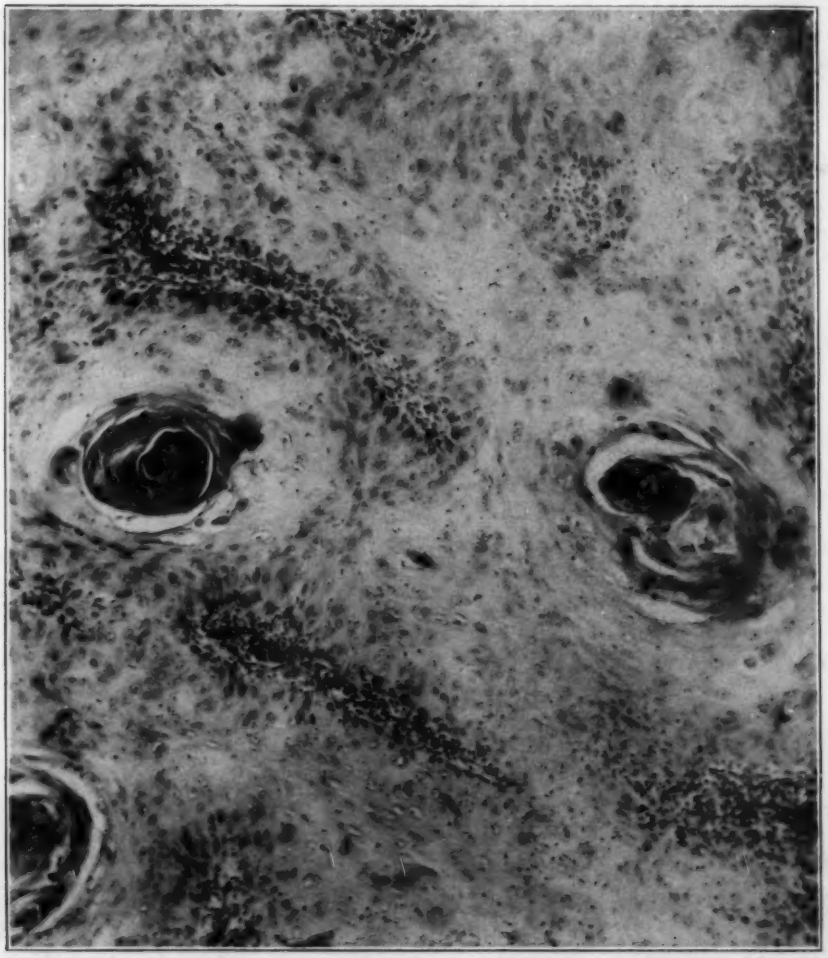

Fig. 27.—Section of growth in Figure 26; typical squamous cell cancer with "pearl" formation.

smooth and reddened, not raised or indurated. It was treated with acid and scabbed over, but did not remain healed. He had twelve of these treatments, from August, 1921, to January, 1922. Since January, 1922, there had been a very rapid increase in size of the lesion. There has been itching but no real pain.

Examination.—There was a raised area, roughly from 1.5 to 2 cm. in diameter, on the left side of the face, just above the malar bone. The growth appeared

like granulation tissue and stood from 0.5 to 1 cm. above the surrounding skin. There was slight infiltration of the skin about the tumor, but the neighboring glands were not enlarged. The Wassermann reaction was negative (Fig. 26).

Treatment.—Excision of the tumor was done, under local anesthesia. The surrounding regions were treated by roentgen ray.

Microscopic examination showed well marked squamous cell carcinoma (Fig. 27).

Fig. 28.—Exuberant growth, which came up quite rapidly following an injury, diagnosed as typical squamous cell cancer. The growth was resected and skin was grafted with good result.

CASE 26.—*History.*—C. P., a woman, aged 72, admitted to the hospital, May 9, 1921, said that, twelve years before (1909) while cutting wood, a splinter had struck her on the nose and caused a small wound, which healed over with a scab. This crust remained without change. Nine months before, she had picked this crust off. Following this, a growth developed which progressed until it involved nearly the whole nose. It was practically painless, but there was sometimes a feeling as if it were full of needles. Recently, she had had a dull aching pain in the frontal region. The growth bled very readily if injured. She had had one roentgen-ray treatment before admission.

Examination.—There were a few seborrheic warts on the right cheek. The growth on the nose was about 3 by 6 cm. in diameter and was raised 1.5 cm. above the skin level. It consisted in an irregularly outlined fungating mass, occupying a position that extended transversely across the dorsum of the nose, from the right alar fold to the left inner canthus. The margins of the tumor were slightly elevated and indurated; the tumor itself was covered by a thick, brownish red crust, except for some places where this had been removed, leaving an underlying tissue that resembled granulations and bled very easily. The lesion was not attached to the nasal bone or cartilages, as it could be moved readily with the skin. There was tenderness on pressure over the left frontal sinus. One small palpable gland was felt in the left submaxillary region (Fig. 28).

The Wassermann reaction was negative.

Fig. 29.—Squamous cell cancer of hand. The axilla was not dissected, in this case, because of the heart condition.

Treatment and Course.—May 14, 1921, excision of the epithelioma was done, under local anesthesia. June 8, this was entirely healed, with an excellent cosmetic result. Skin was grafted on the raw surface at the primary operation.

March 27, 1923, the condition was excellent, and there had been no recurrence. June 8, 1924, there had been no recurrence, and the scar was scarcely perceptible.

Microscopic examination showed well marked characteristics of papillary squamous cell carcinoma. There was a superficial zone of necrosis, from 1 to 2 mm. thick, due to the massive roentgen ray dosage given ten days before operation.

CASE 27.—*History.*—C. B., a man, aged 85, admitted to the hospital, July 22, 1921, said that, four years before, he had noticed a small pimple on the back of the left hand. He squeezed it and pressed out quite a little pus. It was incised several times, and caustics were applied. The hand became swollen,

but the swelling subsided, leaving a small ulcer. This ulceration grew slowly to the size of a 50 cent piece. It never pained and caused no trouble.

Examination.—Mitral insufficiency was noted. There was a flat growth on the back of the left hand between the third and fourth fingers, partially involving the bases of these fingers. The lesion was 3 cm. in diameter, with a flat, partly granulating, easily bleeding surface, and was attached to the skin by a broad pedicle. There was no glandular enlargement at the elbow or axilla (Fig. 29).

Treatment and Course.—July 25, excision and skin grafting were done under local anesthesia. A microscopic examination showed squamous cell carcinoma. The site of the operation healed. There has been no recurrence to the present, March, 1923.

Fig. 30.—Squamous cell cancer of ear. Cautery excision was done. The cartilage was invaded. Radium had no effect.

CASE 28.—*History.*—J. C., a woman, aged 61, first seen, Jan. 24, 1924, stated that, about one year before, a small scab had come on the top of the right ear. The scab fell off at times but always reformed, and the sore began to increase in size. There was considerable discharge of a watery nature, which later became purulent. The growth of the sore was quite rapid, so that the whole top part of the ear was involved.

Examination.—The whole upper part of the right ear was involved in a growth, 4.5 by 2 cm. The lesion had the appearance of bright red granulation tissue with a whitish blue, raised, everted edge, about 0.5 cm. above the surrounding skin. There was considerable seropurulent discharge, and no glands were palpable in the neighborhood. There were many patches of senile keratoses on the face (Fig. 30).

The Wassermann reaction on the blood was negative.

Treatment and Course.—Two applications of radium were made without the slightest observable effect. March 28, the top of the ear was amputated with cautery, under nitrous oxid and oxygen anesthesia. There was a typical squamous cell cancer with deep infiltration and destruction of the cartilage. The wound has healed perfectly, with no recurrence to date, August, 1924.

Case 29.—*History.*—M. Q., a man, aged 64, first seen, Sept. 2, 1923, was admitted to the hospital for syphilitic and rheumatic heart disease and heart failure. The scar with ulceration was noted in the physical examination. The scar had been present for years; the ulcers were relatively recent in formation.

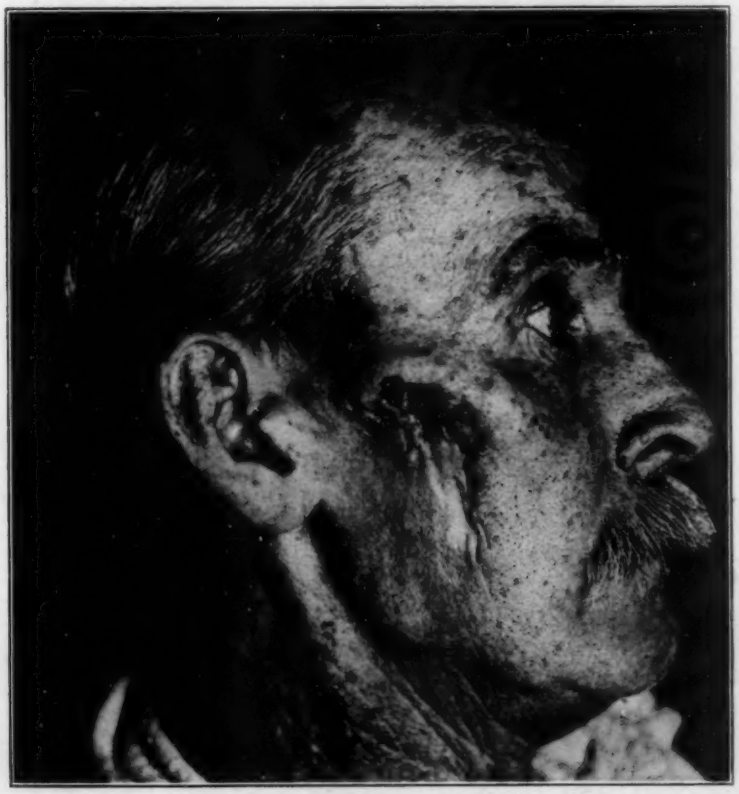

Fig. 31.—Squamous cell cancer arising in old scar. The ulcerations may be multiple.

Examination.—There was a depressed scar, 6.5 cm. long by 2 cm. wide, extending vertically from the right malar bone to the midportion of the cheek. The upper portion of the scar had a deep ulceration, 2 cm. long, with hard, raised edges and a clean, granulating base. There were two other smaller ulcers with similar characteristics on the anterior margin of the old scar at its midportion. There were many patches of senile change in the skin of the face. No palpable glands were made out (Fig. 31).

The blood Wassermann reaction was 4 plus.

Course.—The patient died of heart failure.

SACRAL ANESTHESIA

SOME PRACTICAL AND EXPERIMENTAL POINTS

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Sacral anesthesia was first introduced by Cathelin and was later popularized by Laewin. During recent years, it has come into general use. The terms "caudal" and "epidural" have also been applied to this method of obtaining anesthesia. It consists in the introduction of the anesthetic solution into the lower portion of the bony sacral canal. The fluid disseminates laterally along the course of the spinal nerves, producing conductive anesthesia. The investigations of Thompson in 1917, Brenner in 1923, and others have shown the approximate routes taken by the fluid when injected into the cadaver. Careful checking up of anesthetic areas following the introduction of varying amounts and varying concentrations of procain has been carried out by a number of observers. Harris, Thompson, Kappis and others showed, for instance, that when solutions containing dyes were injected into the sacral canal the nerves in the lower cervical region of the cadaver were reached. Thompson used 30 c.c. of an aqueous eosin solution. Clinically it has been noted that anesthesia remote from the point of injection has occurred. However, the nerves constituting the sacral plexus alone are most affected. Not infrequently the lumbar plexus shows varying degrees of anesthesia, and occasionally writers have noted anesthesia in the nerves higher up.

In 1916, during a routine charting of the anesthetic areas resulting from this method, we found that after the introduction of 75 c.c. of 1 per cent. procain-epinephrin solution there was the appearance of complete anesthesia bilaterally as high as the nipple line. This observation was made in the case of a man 62 years of age in whom a Kraske operation for carcinoma of the rectosigmoid was performed. In numerous other instances, we have noted the appearance of anesthesia, often irregular and incomplete, in the region of the thoracic nerves.

The appearance of this phenomenon may perhaps be due to numerous factors acting alone or in combination. The amount of solution injected in comparison to the capacity of the epidural space, the concentration of the solution, the rapidity with which it is introduced and finally the position in which the patient is placed during, or directly after, the injection may have some bearing on the results. The resistance of the structures surrounding the nerve tracts as they pass laterally from the spine compared with those of the epidural space as the fluid advances in an upward direction also may be a factor of more or less importance. One may assume further that the fluid will probably disseminate in the

living subject in a manner that is at variance with that found in the embalmed cadaver.

In an effort to obtain a more or less graphic picture of the results following the introduction of fluid into the epidural space through the sacral foramen, the following experiments were carried out.

Fig. 1 (Experiment 1).—Sacral canal after injection of 30 c.c. of saturated solution of sodium iodid (plus 30 c.c. of 15 per cent. solution of sodium iodid), showing needle-point deflected to left; shadow of solution reaches fourth lumbar vertebra; greatest intensity at upper portion of sacrum.

PROTOCOLS

EXPERIMENT 1.—An unembalmed body, twelve hours after death, was used for this experiment. One ounce (30 c.c.) of 15 per cent. sodium iodid solution was injected epidurally and a roentgenogram was immediately made. This and all subsequent roentgenograms were taken with the body in the lateral

horizontal position. It was found that the solution used (15 per cent.) was not sufficiently concentrated to demonstrate clearly the course taken by the injected fluid. I therefore used a saturated solution of sodium iodid (100 per cent.), and after introducing an additional ounce of this solution a roentgenogram (Fig. 1) was made. We then injected another ounce of the solution, and another exposure (Fig. 2) was made. Figures 3 and 4

Fig. 2 (Experiment 1).—Slightly wider distribution of solution in upper sacral region after injection of 59.2 c.c. of saturated solution of sodium iodid (plus 30 c.c. of 15 per cent. solution of sodium iodid); solution now reaches top of first lumbar vertebra, apparently distending epidural space but not yet disseminating lateralward in lumbar region.

show the roentgenographic findings after the injection of 3 ounces (89 c.c.) of the saturated solution plus 1 ounce (30 c.c.) of 15 per cent. solution. Unfortunately the exact upper levels that our solution reached in the first experiment were not obtained, our interest being focused on the sacral region,

but a single plate of the upper spine taken after the total amount had been injected, Figure 5, shows the solution reaching the upper cervical vertebrae. Figure 4 shows the sacral and lumbar regions after the injection of 4 ounces (118.4 c.c.) in Experiment 1. (Comparison should be made with Figures 1 and 2.)

EXPERIMENT 2.—For the purpose of this experiment the unembalmed body twelve hours after death was used. Figure 6 shows the lumbar and sacral

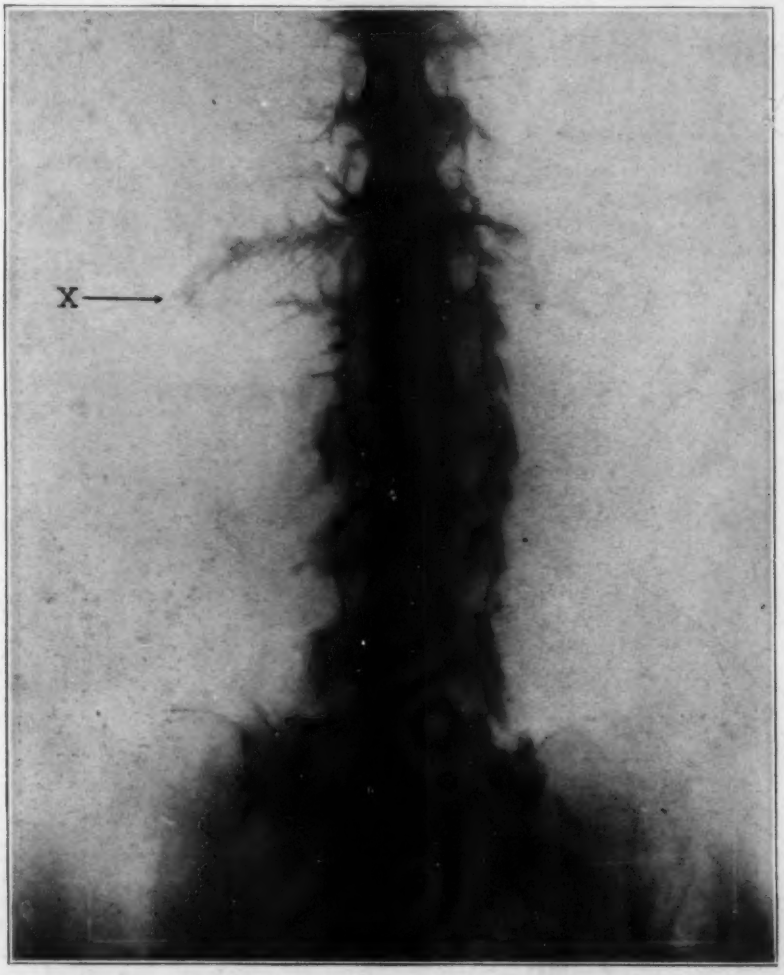

Fig. 3 (Experiment 1).—Increased density in sacral area after injection of 89 c.c. of saturated solution of sodium iodid (plus 30 c.c. of 15 per cent. solution of sodium iodid). The solution has disseminated lateralward in lumbar and lower thoracic region. *X*, marked extension of solution along eleventh thoracic nerve on right side.

regions after the injection of 3 ounces (89 c.c.), but it will be noted that the fluid does not extend laterally to the degree shown in Figure 3 of Experiment 1, in which the same amount of saturated solution plus 1 ounce (30 c.c.) of 15

per cent. solution was used. Figure 7 shows the height that the solution reached after the injection of 3 ounces (89 c.c.), the region of the fourth thoracic vertebra. It will be noted that lateral extension of the solution is much less marked than in Figure 3, in which case the extra ounce of weak solution was injected.

From the roentgengraphic findings it will be noted that the fluid injected into the sacral canal traveled with great rapidity upward along the epidural

Fig. 4 (Experiment 1).—Sacral and lumbar regions after injection of 118.4 c.c. of saturated solution of sodium iodid (plus 30 c.c. of 15 per cent. solution of sodium iodid); increased density in both regions. Comparison should be made with Figures 1, 2, 3 and 4.

space, even to the cervical vertebra (Fig. 5). It is also evident that, as the amount of the injected fluid increased, the shadow in the sacral and lumbar regions increased both in intensity and width (Figs. 1 to 4). In Figure 3, which was taken after the injection of 3 ounces (89 c.c.) of saturated solution

of sodium iodid plus 1 ounce (30 c.c.) of 15 per cent. of solution, a shadow may be seen extending 4 or 5 inches (10 or 12 cm.) laterally in the region of the eleventh thoracic nerve. A similar lateral diffusion can be seen along the cervical nerves, Figure 5, after the injection of 4 ounces (118.4 c.c.) plus the extra ounce of weaker solution.

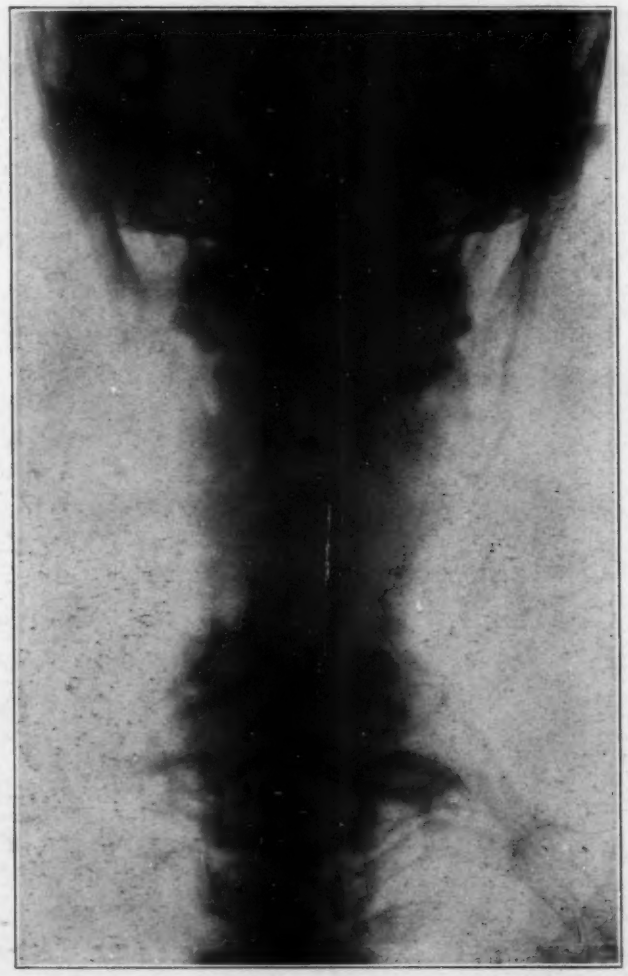

Fig. 5 (Experiment 1).—Cervical and upper thoracic regions after injection of 118.4 c.c. of saturated solution of sodium iodid (plus 30 c.c. of 15 per cent. solution of sodium iodid); solution makes a dense shadow in upper cervical and upper thoracic regions; shadow is less dense in lower cervical region; lateral extension of solution in upper thoracic region.

Just what conclusions may be drawn from these experiments it is difficult to say. It is certain that the instillation of 4 ounces (118.4 c.c.) of fluid into the sacral canal of the fresh (12-hour) cadaver results

in the dissemination of a considerable portion of the fluid as high as the origin of the cervical and thoracic nerves. It is equally certain that the fluid injected (with slight pressure only) meets with much less resistance in the epidural space than that encountered along the sheaths

Fig. 6 (Experiment 2).—Lumbar and sacral regions after injection of 59.2 c.c. of saturated solution of sodium iodid. Intensity of shadow in sacral region corresponds approximately with that of Experiment 1, Figure 3. Epidural space contains solution up to third thoracic vertebra. Almost no extension lateralward. Comparison should be made with Figure 3 of lateral extension in lumbar and lower thoracic regions.

of the sacral nerves as they extend laterally. The findings further explain the rationale of the appearance of anesthesia at exceptionally high levels in certain instances. They further explain an observation

that we have occasionally made that when the solution is injected with rapidity it is not uncommon to have the patient complain of paresthesia in the regions supplied by the lumbar or even the thoracic nerves. These findings might likewise fortify the opinions of those who have had large experience with this method and who believe that the solution

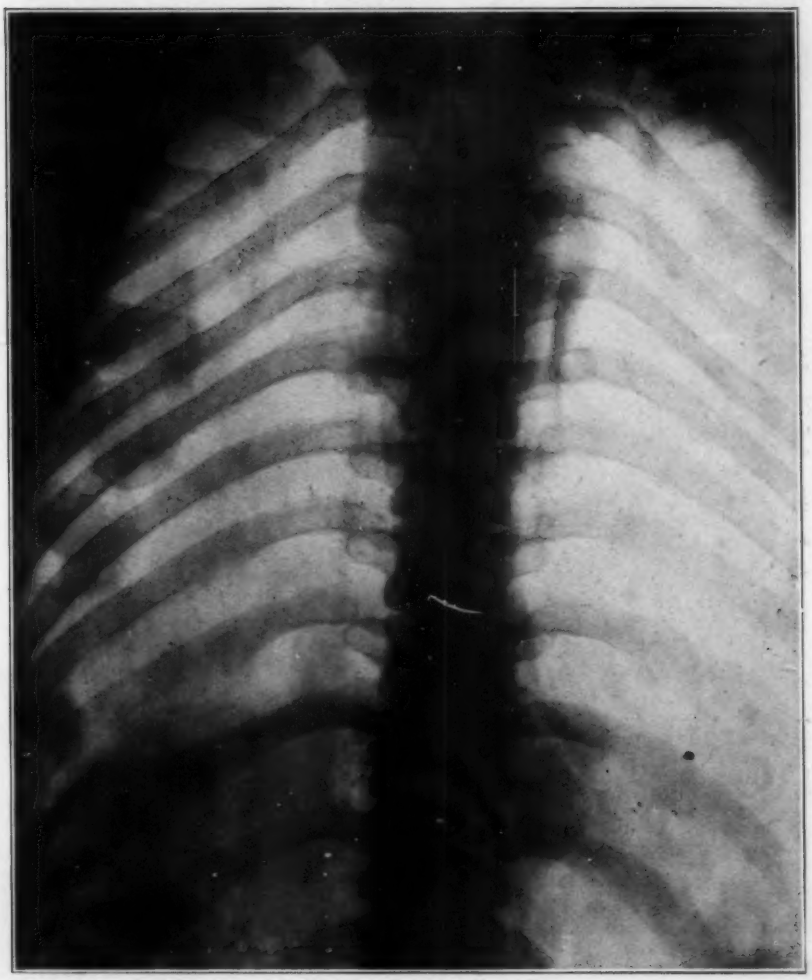

Fig. 7 (Experiment 2).—Lumbar and sacral regions after injection of 59.2 c.c. of saturated solution of sodium iodid, showing level reached by solution; practically no lateral extension. Comparison should be made with Figure 3.

should be injected *slowly*. And yet, we believe these opinions were arrived at on account of the more frequent appearance of toxic symptoms following rapid injections. It is probably also true that the slow

injection of the solution will allow more time for its diffusion in the region of the sacral nerves, thus giving more complete anesthesia in the areas which one desires to anesthetize. It may likewise, in a measure, explain the clinical observation we have made that better anesthesia of the local parts has been obtained since we have abandoned the practice of elevating the patient's pelvis by means of pillows or the knee-chest position while introducing the solution. These experiments further suggest that it is not unreasonable to assume that some simple method of introducing epidural anesthesia by way of the sacral route in higher regions along the spine (lumbar, thoracic or even cervical) is possible of development. It may be conjectured that, with a drug of sufficiently low toxicity, and of great potency, complete anesthesia of all the spinal nerves may yet be established by the introduction of solutions through the sacral canal.

Aside from the toxicity and potency of the drug, the rapidity of its introduction, and the plane on which the patient's body is placed may in the future be considered more important factors than they have been in the past.

With increased experience, the margin of error in obtaining sacral anesthesia has been greatly reduced. Tortuosity of the canal is no longer to be considered much of an impediment. The use of malleable material has practically eliminated the danger of breaking off needles in the canal. Slow injection of the solution has markedly reduced toxic symptoms, and the realization that the introduction of 3 or even 4 ounces (89 or 118.4 c.c.) of a 1 per cent. procain-epinephrin solution is safe, provided proper precautions are observed, has resulted in the establishment of complete anesthesia in a high percentage of cases. In addition to its effectiveness in surgery of the rectum, vagina and bladder, its aid in abdominopelvic operations is of undoubted merit. The experiments referred to above would seem to indicate that the assumption of the Trendelenburg position, which is so desirable in pelvic surgery, would be favorable to bringing the anesthetic solution into contact with nerves supplying the upper field. This would materially reduce the normal sensitiveness of the pelvic structures.

During the last nine years, I have investigated the effect of introducing various amounts of procain solution in different percentages. From 1 to 4 ounces (30 to 118.4 c.c.) of 0.5 per cent. solution, from 1 to 4 ounces of 1 per cent. solution and from 1 to 2 ounces (30 to 59.2 c.c.) of a 2 per cent. solution have been used over considerable periods and in a comparatively large number of cases. Theoretically, a smaller amount of the more highly concentrated solution should give the more satisfactory low anesthesia, and yet my impression until recently has been that the anesthesia obtained after the injection of

from 3 to 4 ounces (89 to 118.4 c.c.) of 1 per cent. solution gave universally better results than when from 1 to 2 ounces (30 to 59.2 c.c.) of a 2 per cent. solution was used. However, as several years have elapsed since the stronger solutions were injected as a matter of routine, I am at present testing the latter method in an effort to obtain sufficient evidence from which to draw conclusions. It would seem that the bathing of the sacral and lumbar nerves in a 2 per cent. solution of procain should result in a quicker and more intensive anesthesia than employment of the weaker solutions, and yet it may be possible that the complete distention of the epidural space with a larger amount of the solution might be the means of forcing the injected fluid laterally along the course of the nerves to a greater distance. Our roentgenograms (Figs. 1 and 4) conclusively demonstrate that the shadow produced by the fluid is considerably broader in the sacral region when 4 ounces (118.4 c.c.) are indicated than when only 1 or 2 ounces (30 or 59.2 c.c.) have been introduced.

At this point I might digress for a moment and call attention to one factor which may be of great importance in estimating the results obtained when using any form of local anesthesia. I refer to the "personal equation." Until the time arrives when the establishment of satisfactory local anesthesia means complete abolition of pain sensation, the reports of different observers, as they pertain to supposedly identical technic, will be certain to vary in some degree.

TECHNIC OF ADMINISTRATION

The technic of the administration of sacral anesthesia is comparatively simple and has been so frequently described and illustrated in the literature that only a few points that we consider of special importance will be stressed.

Position of Patient.—The various positions of the patient that have been recommended, the knee-chest, the elevated pelvis, the lateral, and the prone with the patient's face downward have been tested out. My preference is for the prone position without the elevation of the hips. The patient's back should be exposed well up to the thoracic region. I usually make the injection with the patient lying on the stretcher after which he may, by turning over, lie directly on the operating table.

Asepsis.—We employ tincture of iodin in 3.5 per cent. solution for the purpose of sterilizing the skin, and the utmost precautions are taken to prevent the solution from reaching the anal region, the effect of which is most irritating to the patient.

The exposure of the patient's back makes the midline evident as a guide when introducing the needle.

After identifying the landmarks a wheal should be made, using a fine 2 or 2½ inch (5 or 6.2 cm.) needle. The needle should now be introduced carefully until its point reaches the sacrum. Here a generous amount of the solution should be deposited and the sacral hiatus searched for with the needle-point. All sensitiveness should be allayed by injecting each time the needle contacts with the bone. Generally after a few attempts, this fine sharp needle will enter the canal through the sacrococcygeal ligament. The syringe is then detached from the needle and a larger needle is introduced, the fine one, which has been left in situ, being used as a guide. It is well to force a few drops of fluid through the large needle before introducing it for the purpose of washing out the débris (oxids) that has collected within its lumen as well as to insure its patency. It is not necessary to introduce the needle any great distance into the canal. The next step is to make suction on the needle by withdrawing the plunger of the syringe. As a rule, a few air bubbles are seen traveling up through the solution. The next most important detail is to ascertain the degree of pressure required in order to force the solution into the canal. The fluid should flow in with only the slightest amount of pressure. Resistance to the inflow of the solution will usually indicate that the needle is not within the canal or that its point is beneath the periosteum. During the injection, one should be constantly on the lookout for the appearance of a swelling posterior to the needle-point, which would indicate that the needle was behind the sacrum and not in the canal. In my experience failure to enter the canal and to obtain anesthesia has been extremely rare during recent years. The next point is the necessity of introducing the solution slowly. Five minutes of time for each ounce injected is, in my judgment, about the proper cadence.

The elevation of the head or foot of the table will depend on the region we wish to anesthetize.

The amount and strength of the solution to be used will depend on the procedure which is to be carried out, as well as on the local conditions, and the general condition of the patient. To illustrate: An examination of a comparatively normal bladder will require a minimum dose, whereas an inflamed or tuberculous bladder may require the maximum. Likewise when using sacral anesthesia as an adjunct to major pelvic procedures, a rather large dose may be indicated if the general condition of the patient warrants it.

The objections to the method are the possibility of encountering bony anomalies, the difficulty of detecting the landmarks in the obese, the occasional manifestation of toxic symptoms, psychic disturbances, and the time and irksomeness necessitated in its induction. We have had two cases of mild infection, one requiring incision and drainage of

the soft parts. In the other, an aged diabetic patient showed redness about the point of injection, a slight necrosis of the skin and a discharge of a few days' duration. Many years ago I had the misfortune to break a needle during its introduction and this necessitated the making of a small incision, after which the broken piece was readily removed. The removal of the temper from the needle has met this contingency.

During the induction of sacral anesthesia, the pulse, the color of the patient, the pupils and the blood pressure should be constantly watched, as toxic manifestations are not infrequently noted, when the sacral method as contrasted with other methods of producing local anesthesia is used.

CONCLUSIONS

Sacral anesthesia has become a well standardized procedure.

It presents many advantages and also has some disadvantages.

Its advantages greatly outweigh its disadvantages.

With sufficient training and the employment of a proper technic, the margin of error is slight.

Experiments on the fresh cadaver show that the resistance offered by the tissues occupying the epidural space is not great and that solutions injected even under gentle pressure advance rapidly to high levels.

Theoretically, the strength of the solution, the amount employed, and the position of the patient should influence the intensity and distribution of the resulting anesthesia.

Finally, it is possible that the scope of epidural anesthesia may in the future be made to encompass regions far beyond those which are anesthetized by the methods now in use.

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LEONTIASIS OSSEA AS A MANIFESTATION OF PAGET'S DISEASE

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In one of his classic lectures delivered during the winter semester 1862-1863 at the University of Berlin, Virchow [1] directed special attention to the hyperostoses affecting the facial and cranial bones. He dwelt at length on this localization of bone hypertrophy because it served him well in the discussion of the general subject of periostosis and hyperostosis. For, as he pointed out, these processes when affecting the skull are often of unusual severity and lead to such striking facial and cranial deformities that even in his time there had accumulated a number of famous skulls of unusual size, shape and thickness from which the gross pathology, at least, might be studied. Occasionally, too, an illuminating clinical history accompanied the record.

In this connection Virchow related graphically the case of Forcade.

> Unhappily it was this surgeon's son who was the patient. With the exception of an attack of smallpox the boy had been well until his twelfth year (1734). At this age he developed at the inner canthus of the right eye an abscess of the lachrymal sac which his father incised. Suppuration continued for a long while and coincidentally an almond sized mass appeared on the nasal process of the right superior maxilla. This hyperostosis increased to such an extent that when the boy was 15 years of age the nasal cartilage was so compressed that he could breathe only through his mouth. The disorder extended to the lower jaw in such a manner that only the articular surfaces and alveolar borders retained a normal structure. The upper jaw, the walls of the orbital cavities with the exception of their superior aspects, the nasal openings, the hard palate and the malar bones became involved, swelling to huge shapeless masses. In his twentieth year the young man's face was monstrous. Exophthalmos, myopia, difficulty in speech and a general enfeeblement supervened; blindness followed, the patient dying of tuberculosis in his forty-fifth year. The macerated head weighed eight and a half pounds, the lower jaw, three pounds, three ounces. Large tuberous and ragged exostoses of marble-like density projected from the lower jaw and from the inferior borders of the orbital cavities. The bones of the cranium were thickened and exhibited small, flat, completely sclerosed excrescences. The frontal sinuses and antra were entirely obliterated. The remainder of the skeletal system was remarkable for its contrasting delicacy. Let it be noted that at the section the facial muscles had assumed a fibrous appearance and had coalesced with the cellular tissue and the periosteum.

1. Virchow: Die Krankhafte Geschwülste **2**:21, 1864-1865.

To this state of the skull, arising he knew not how, Virchow applied the name leontiasis ossea; not because the victim presented a facial resemblance to the lion but because he thought that "these hideous disorders of the skeletal system" were analogs of a "leontiasis" of the soft parts as exemplified by the connective tissue hyperplasia of fibroma molluscum or elephantiasis mollusca, conditions which do give the facies a leonine aspect.

In time, many examples of malformations of the skull with their concomitant facial deformities were described under Virchow's title but it gradually became clear that the group contained a diversified lot of pathologic conditions from which such obvious entities as osteosarcoma, osteomas, gummas, odontomas and the acromegalic syndrome could be excluded. There remained, however, examples of periostoses and hyperostoses chiefly or exclusively affecting the bones of the skull to which the term leontiasis ossea was still applicable.

Under this caption Ramijean [2] in France in 1921 gave the results of his study of this condition; Sternberg [3] in Germany contributed the article on leontiasis ossea in Nothnagel's System; Kanavel [4] in this country reviewed the subject in 1907 and most recently in England, still using the same title, Knaggs [5] has published an important article, beautifully illustrated.

It is a curious fact that in neither the American nor the English article is it suggested that some of the cases of leontiasis ossea are examples of osteitis deformans, the disorder which Paget [6] described in 1877. Indeed, Kanavel states that "a relation (of leontiasis ossea) to . . . osteitis deformans of Paget cannot be supported." [7] Yet, a few pages preceding Kanavel's review is Beck's [8] report of a case of leontiasis ossea, with illustrations depicting in typical fashion a victim of Paget's disease with thickened clavicles, deformed thorax, the characteristic transverse abdominal sulcus, the curved thighs, but with one of the facial malformations of leontiasis ossea. Years before, on the other hand, Prince had concluded that "we have no sure ground for differentiating hyperostoses cranii from osteitis deformans." [9] Our patient, like Beck's (to whom she bears what may be called a strong family resemblance),

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2. Ramijean: La Leontiase Ossea, Thèse, Paris, 1921.
3. Sternberg: Nothnagel's System, Vegetationsstor. u. Systemerkr. der Knochen **7**:22, 1903.
4. Kanavel: Surgical Intervention in Leontiasis Ossea, Surg., Gynec. & Obst. **4**:719, 1907.
5. Knaggs, R. L.: Leontiasis Ossea, Brit. J. Surg. **11**:347 (Oct.) 1923.
6. Paget: Med.-Chir. Tr., London, **60**:37, 1877.
7. Kanavel (Footnote 4, p. 720).
8. Beck, Carl: Surg., Gynec. & Obst. **4**:710, 1907.
9. Prince: Tr. A. Am. Phys. **17**:382, 1902.

exemplifies this identity of at least one group of the cases of leontiasis ossea with Paget's disease. To substantiate this opinion one must rely on the clinical investigation of the bones together with the findings disclosed by the roentgenologic examination. For with the introduction of the latter method, a roentgenographic picture characteristic of Paget's disease has been established. Most typical is the roentgenogram of the skull (Fig. 1).

Baetjer and Waters have described in the space of a page of their work on "Injuries and Diseases of the Bones and Joints" (1921) the roentgenoscopic changes of osteitis deformans, and their account of the cephalic shadow serves to describe the roentgenogram of our patient's head reproduced here. It shows "round, knobby-like masses of bone lying between the inner and outer tables of the bone; sometimes these

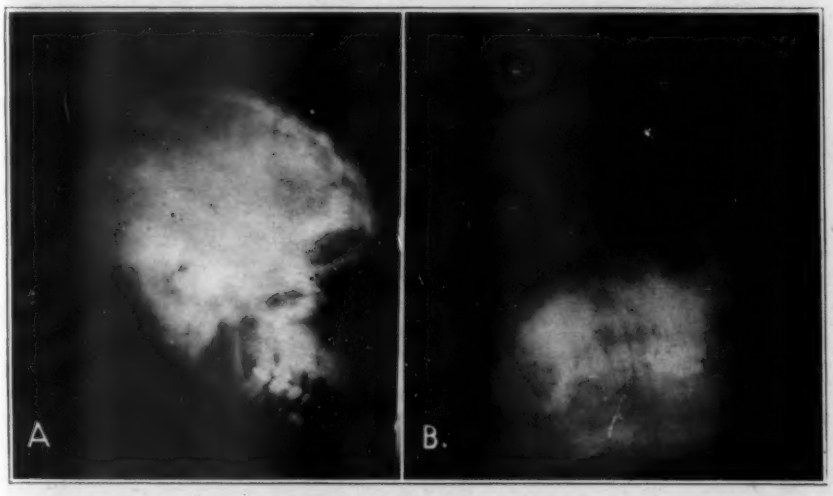

Fig. 1.—Skull showing, *A*, "curled kinky hair" appearance and, *B*, hyperostotic deposits of upper jaw obliterating maxillary sinuses.

will be on the outer table. . . . The best description of this condition is to imagine the curled kinky hair of the negro to have undergone calcification."

Perhaps "the curled kinky hair" shadow in the roentgenogram in Paget's disease corresponds with the "coarse woollen cloth" appearance that Knaggs [10] describes in a case of leontiasis ossea. He explains the production of this appearance by the protrusion of little buds of osteogenic tissue from the medulla through apertures in the bone and the subsequent ossification of these projections.

The changes of osteitis deformans are also revealed by the roentgenogram of the bones of the legs of our patient (Fig. 2).

10. Knaggs (Footnote 5, p. 362).

Clinical examination of her osseous system supports, too, the opinion that we are dealing with Paget's disease. Besides the changes in the cranial and facial bones, the clavicles are thickened and tender; so, too, are the upper thirds of the humeri; there is increase in the antero-posterior curve of the spine. Both tibias are bowed anteriorly, are tender to the touch over their anterior surfaces and there is here local elevation of temperature without redness. Paget himself mentions "increased heat" at the tibias.

While, therefore, the present instance of leontiasis ossea may be classified as Paget's disease it must be understood that there have been formulated clinical criteria to differentiate the cases recorded as leontiasis ossea from osteitis deformans. Above all it is the discrepancy in

Fig. 2.—Bowing of tibias and thickening of cortex with areas of porosis characteristic of osteitis deformans (Paget's disease).

the age incidence of the two disorders so named that is the most striking differential fact given. Two of the tragic features of the deformation of leontiasis ossea are that in the majority of the published cases it is said to begin in early life, congenitally, in childhood or about puberty, and that the cranial and especially the facial bones are almost exclusively involved.

On the other hand, in Paget's publication one reads "at present with the exception of the seventh case this disease has been observed as beginning only in persons over 40 years old." [11] Perhaps with the additional

11. Paget: Med.-Chir. Tr., London, **65**:225, 1882.

aid of the roentgenologic examination Paget's disease will in future observations be found earlier in life and involvement of bones other than those of the head will be more frequently disclosed.

Confirmation of this prediction is offered even now by Knaggs' observation of leontiasis ossea in a child in whom lesions in the long bones would have been overlooked if roentgenoscopy had not been employed.[12]

The report deals with a case of a boy, aged 6½, with enlargement of the left temporal bone which was thought to be sarcomatous. A section proved it to be of an inflammatory nature. About a year and a half later there was proptosis. Small bosses appeared on the right frontal and parietal bones. The left half of the inferior maxilla was involved. Skiagrams showed discrete rarefied patches in most of the long bones. These were more numerous in the bones of the hand and wrist.

A recent publication (1924) by J. Naito entitled "Die Hyperostosen des Schädels" is not accessible to us but it should be informative along the roentgenoscopic aspect of the present subject since eighty-four roentgenologic plates accompany the text.

If there were a pathognomonic histologic picture of Paget's disease or a known etiologic agent the problem of the relation of the deforming chronic inflammations of the bones in the young to osteitis deformans of later years could be settled. But the cause of Paget's disease is unknown and there is no unanimity as to a histology specific of the malady. There are exhibited lesions of rarefying and proliferative osteitis with signs of decalcification and of absorption, with subperiosteal new bone formation and osteoid tissue of myelogenous origin with evidence of calcification, or the medullary substance may be replaced in areas by vascular connective tissue.

Similarly, the bones of the skull in leontiasis ossea and the long bones when lesions in them have been detected and examined show this varied histologic picture of chronic inflammation peculiar to osseous tissue.

Knaggs [13] has attempted to clarify the situation in leontiasis ossea by classifying the majority of the cases in two groups: (1) Very chronic periostitis spreading slowly from bone to bone to which the title of creeping periostitis of the bones of the face and skull may be given. (2) Diffuse osteitis of the bones of the face and skull which (*a*) may affect all the cranial and facial bones; (*b*) may be localized to one or more bones or a part of one, and (*c*) may affect one or both jaws and rarely spread beyond. The histology of this second group is in almost all instances that of osteitis fibrosa.

12. Knaggs (Footnote 5, p. 371).

13. Knaggs (Footnote 5, p. 348).

As corresponding with this anatomic classification Knaggs [14] suggests for the first group the etiologic relation of infections of the nasal fossae and paranasal sinuses to the creeping periostitis because of the frequency with which the hyperostosis begins near these fossae; while he attributes the lesion of osteitis fibrosa of the second group to "toxins" circulating in the blood.

These considerations are, however, still theoretic since no microorganism has been isolated from the periostitic deposits and the nature of the "toxins" is not even indicated except when the disorder affects only the jaws, when it is assumed that they have a local origin, namely, "in some septic trouble about the teeth." It is difficult to conceive how infections or what is ordinarily understood by "circulating toxins" could produce a condition limited to the osseous system without assuming some peculiar predisposition on the part of the individual affected.

It is fascinating to speculate whether an endocrinopathy may in some cases furnish the necessary underlying diathesis; or may, in others, a dysfunction of one or more of the glands of internal secretion be the effective cause of leontiasis ossea? An analogy is afforded by the hyperfunctioning of the glandular anterior lobe of the pituitary body in the production of the hyperplastic changes in the osseous system of the acromegalic subject.

A further suggestive condition but less well understood is the degenerative nutritional disturbance of the bones in the osteomalacia of pregnancy and of puerperium in which the ovaries, the thyroid or the parathyroid in abnormal functioning have been each or severally accused as causal factors.

Long before endocrine disturbances were assumed to exist in pregnancy and in the puerperium a connection between the latter and exostoses of the skull had been admitted and the "puerperal osteophyte" was the subject of repeated investigation.

Virchow [15] quotes the case of a woman, aged 38, who after her seventh delivery developed with repeated headaches a small tumor in the temporal fossa. With each succeeding puerperium—and there were four more—the tumor showed an increase in size, its growth being accompanied by severe headache, vertigo, unconsciousness, vomiting, and, finally, paralysis and death, in seven years. At necropsy an ivory-like bony nodule an inch (2.5 cm.) thick was found in the lateral portion of the frontal bone covered on both its inner and outer surfaces with more porous masses. Its inner aspect was lined with numerous sharp and blunt osseous projections.

In each of the preceding disorders adduced to show the effect on the bony system of what is presumably an endocrinopathy, the thyroid is frequently grossly altered. In acromegaly it is almost always changed;

14. Knaggs (Footnote 5, pp. 377-378).
15. Virchow (Footnote 1, p. 36).

goiter and osteomalacia have frequently been associated, while exophthalmic goiter has often had its inception in pregnancy and the puerperium.

The foregoing considerations have been brought forward as a prelude to the statement that our patient suffering from leontiasis ossea first observed the enlargement of her upper jaw during her only pregnancy twenty-eight years before and that she had a struma of moderate size and of nodular character. Two of her sisters also present goiters.

A goiter which resembled in microscopic structure the thyroid gland of the exophthalmic variety was found in one of Knaggs' patients whose head began to enlarge at the age of 7 years and who died of diphtheria at 21.[16]

After all is said, the etiology of leontiasis ossea and, therefore, of at least one variety of Paget's disease remains undetermined though there is some evidence on the one hand of its infective origin and there are arguments from analogy, on the other, which suggest that endocrine dysfunctioning is responsible for the malady.

Better established is the clinical course, including signs and symptoms, for these can be reconstructed from the recorded histories and from illustrations of museum specimens. It is the enlargement of the head that usually first attracts attention. Many modes of misshapen heads are represented according to the region of the skull on which the bony deposits are most prominent. When the lower jaw comes to protrude far forward in a high degree of prognathism a resemblance to the gorilla has been suggested. The protruding upper jaw like that of our patient recalls the snout of many of the lower animals, while the skull of Forcade's son, with its enormous malformed inferior maxilla, the huge mammillated spheres of bone arising from the upper jaw and malar bones obliterating the nasal cavities and almost shutting off the orbits, resembles the head of neither man nor beast! Include the bowing of the back when the vertebral column is attacked and the bending of the lower limbs when their bones are affected and the picture of the deformity is almost complete. In some cases there is to be added exophthalmos caused by the pushing of the eyes forward or downward through pressure of the intra-orbital bony excrescences.

Involvement of the general health of the sufferer from leontiasis ossea is not characteristic. The lesions being almost entirely confined to the skull it follows that the symptoms are to be correlated with encroachment on the intracranial contents, with the contraction of the orbits and nasal fossae and with pressure on vessels and nerves through the narrowing of the cranial foramina. Therefore, headache and dizzi-

16. Knaggs (Footnote 5, p. 366).

ness are common complaints in the developed disorder, though pain in the head may be the earliest discomfort. More serious cerebral symptoms, convulsions, paralysis, mental retardation and psychoses are recorded in the literature.

The special senses of sight, hearing and smell may be affected. Choked disk and a resultant atrophy have been observed and may arise not only from an increase in intracranial pressure but from the compression of optic nerve and artery by the bony deposits narrowing the optic foramen. The globe itself may be destroyed through interference with its nutrition. All degrees of impairment of hearing have been associated with the disorder. The deafness is of the otosclerotic type and has been the subject of two recent articles [17] in connection with the more common forms of osteitis deformans. Anosmia also is occasionally noted. Dacryocystitis is now and again mentioned and appears to be secondary to stenosis of the tear duct.

Headache and dizziness were prominent symptoms in the present case and a parasthesia described as a sensation of "crawling" in the right half of the face was an annoying feature. The patient's vision was almost perfect. There was a very low degree of hyperopia, the eye-grounds appeared normal. There was complete obstruction of the left nasal fossa and of the corresponding maxillary sinus, due to hyperostotic deposits. The hearing was markedly impaired, the tick of a watch held to either ear was not perceived. The patient's memory was poor, she was apathetic and irritable.

The evolution of leontiasis ossea is slow and generally progressive. When only one bone or a part of one has been involved it may be assumed that the process has come to an abortive termination. The patients live through a period usually measured in decades, from one to four.

The end is brought about by a terminal infection or occasionally by a premature cerebral hemorrhage. Sarcoma has developed on the basis of the long standing hyperostotic lesion. Obviously, in the present state of our knowledge relief of symptoms is all that can be offered these patients.

Ablation of bony masses obstructing the cranial fossae and decompressive operations for the relief of increased intracranial tension suggest themselves as palliative measures when indicated. As a matter of fact, a few such operations have been undertaken with relief symptoms. This phase of the subject has been critically reviewed by Kanavel.[4]

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17. Jenkins, G. J.: J. Laryngol. & Otol. **38**:344 (July) 1923. Jones, L. W.: Deafness and Its Association with Osteitis Deformans, J. A. M. A. **84**:86 (Jan. 10) 1925.

For cosmetic purposes operation has also been successfully undertaken. Abbe [18] reports a case of Paget's disease with the facial deformity of leontiasis ossea like that exhibited by Beck's patient and by our own in which "a bold and successful operation restored a lawyer to useful life."

> The patient for many years had been the victim of an enormous overgrowth of the alveolar roof of the mouth which produced a repulsive change in his countenance. Abbe removed from the anterior portion of the upper maxilla a block of bone an inch (2.5 cm.) thick. The repair was excellent; a dental plate was successfully adjusted four months later, and a "restoration of physiognomy to that of twenty years before was the happy outcome of the surgical work."

These palliative surgical procedures form the only treatment of the condition bearing the name which Virchow gave to it.

Fig. 3.—Facial appearance of patient twenty-eight years after onset of leontiasis ossea.

Leontiasis ossea is still a useful term descriptive of hyperostosis of unknown origin, and of rare occurrence, chiefly affecting the skull. Roentgenologic study of the skull and other bones and the result of their clinical examination justify the inclusion of the present example in the group of deforming osteitis that bears Paget's name. The etiology of leontiasis ossea is unknown but the fact that in so many instances the disorder begins in or near the nasal and paranasal cavities lends support to the view that infection plays a rôle in its origin. Arguments

18. Abbe, R.: Paget's Disease of Bone, J. A. M. A. **70**:371 (Feb. 9) 1918.

from analogy suggest that endocrine disturbances may contribute another causative factor. The history and the results of the physical findings in the present case follow:

REPORT OF CASE

Leontiasis ossea of twenty-eight years' duration; onset during pregnancy; roentgenologic study of skull and long bones showed changes characteristic of Paget's disease.

History.—Mrs. X, aged 56, consulted us, July 17, 1924, for a physical examination. The father had died at the age of 68 of "gallstones." The mother had died at 78 years of "grippe." Four brothers were dead; one, aged 3 years, died of scarlet fever; another, aged 27, of pneumonia; the other two, aged 42 years and 57 years, respectively, were paralyzed. Three sisters were living; one had

Fig. 4.—Facial appearance of patient before development of leontiasis ossea.

had a goiter removed; another had a goiter at present. There was no history of any bone disorder or of deformities.

There were the usual diseases of childhood. There had been no unusual susceptibility to colds and no history of sinusitis. The menopause occurred at the age of 48. The patient had one child, a son, aged 28. There had been no miscarriages.

About twenty-eight years before, during her only pregnancy, the patient noticed a change in the shape of her mouth, but having received the reassurance of her dentist she disregarded her altered appearance. Six years later, in 1903, she detected a swelling on the inside of the mouth under the right half of the upper jaw. There was no local pain but she remembers having had a "drawing" sensation in the mouth. Four or five years later, the enlargement of the upper

jaw became externally visible. Iodide of potassium was prescribed but the swelling grew larger. In 1906 the patient's attention was drawn to her legs by very sharp pain localized in them. At that time she found the shin bones a little thicker than they were formerly. Ever since, pain of dull aching character had been present in the legs, which had also gradually bowed. About two years before consultation, impairment of hearing became evident, more marked in the right ear. The auditory difficulty had been progressive. She suffered from pain in the head especially in the occipital region and in the nape of the neck. At times she had a sensation in the right half of the face which she likened to "crawling."

Physical Examination.—The patient was of small build, weighing 116 pounds (52.6 kg.). She exhibited a facial deformity (Fig. 3) in striking contrast to her facial contour at 19 (Fig. 4).

Fig. 5.—Huge thickening of alveolar process of overhanging maxilla and widening of interdental spaces.

The head was large and presented prominent cheek bones and protruding upper jaw with a relative recession of the lower jaw. Palpation of the skull revealed rather prominent parietal bones with overhanging ledges in the region of the external occipital protuberances. There was tenderness on moderately light pressure over the left half of the vertex. The frontal region was not particularly tender. Both zygomata at their temporal ends presented enlargements about the size of a cherry and were quite tender to pressure. On either side of the nose there was a decided fulness which was bony in consistency. The maxillary alveolar processes were much thickened from the dental edge as far up as could be felt by the fingers, the thickness at the lower portion being about 2 cm. The mucous membrane of this region was red and injected but was

not much thickened (Fig. 5). Palpation here produced considerable pain. Pressure over the roof of the mouth did not elicit any unusual tenderness nor were there any abnormal irregularities noted here. The lower jaw was apparently normal. There was a slight thickening of the upper edge of the left clavicle near the sternoclavicular junction. The outer thirds of both clavicles were somewhat thickened and tender. The scapulae were essentially negative. No abnormal thickening was detected over the sternum and the ribs though pressure along the ribs produced pain. The humeri presented no visible abnormalities but on palpation each showed some thickening of its upper third, particularly at the insertion of the pectoralis major where there also was considerable tenderness. The forearms and hands were negative for any bony changes. The spine, when

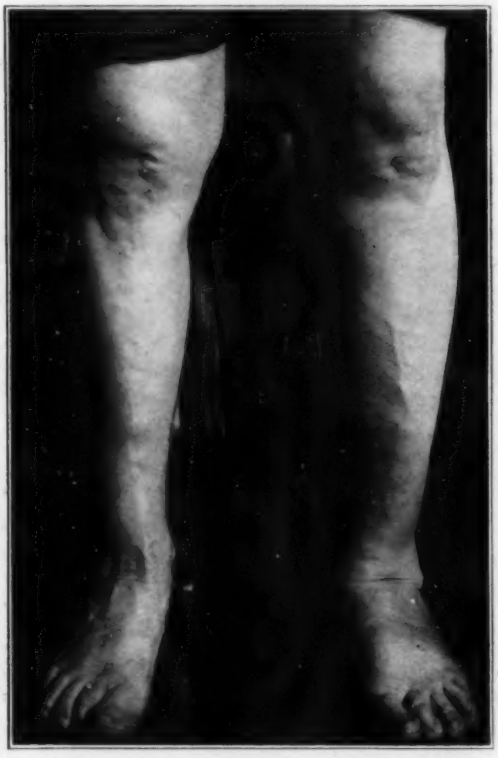

Fig. 6.—Bowing of legs and dilated veins.

the patient was erect, showed slight increase in the anteroposterior curves and slight increase in tonicity of the erector spinae muscles. There was, however, no tenderness over the spinous or lateral processes. There was moderate tenderness at the lumbosacral junction. The ilia presented no unusual prominences and no areas of tenderness. The thighs looked normal and on palpation yielded no abnormal findings. Both tibias were bowed anteriorly but the left was much more markedly bent than the right. Over the front of the legs there was considerable venous dilatation extending over the crests of the bones (Fig. 6). There was no redness but considerable local heat was detected, especially over the right leg. The anterior aspect of each tibia was irregular and in several places

there seemed to be softening of the bony cortex. These soft areas were exquisitely tender. With the exception of a static flatfoot, the feet were negative.

The joints everywhere, with the exception of the right knee, were freely movable, showed no fluid increase, no thickening of the capsule and no local tenderness. The right knee, however, was painful on motion, presented the signs of a thickened capsule and some fluid increase, but the motion was not restricted.

Roentgenologic Examination.—Reference to the films of the skull has already been made in the text (Fig. 1). The upper third of the left femur showed thickening of the cortex with irregular areas of porosis. A similar condition of porosity existed in the lower lumbar spine, in the top of the sacrum, in both innominate bones, especially the right, and in both ischia. The tibias were bowed, the left more markedly than the right. They were thickened and showed longitudinal striae of porosis (Fig. 2).

Additional Physical Examination.—The skin and mucous membranes were somewhat pale; a few dilated venules coursed over the cheeks. There was slight exophthalmos. A partial arcus senilis was present. The pupils were equal and reacted to light and accommodation. The eye-grounds were normal. There was marked impairment of hearing. The temporal arteries were visible and tortuous. The tongue was coated and indented along its border. The gums were retracted. The tonsils were of moderate size; the fauces were negative. Palpation over the posterior cervical triangles elicited pain; in each triangle a moderately enlarged lymphatic gland could be felt. The region of the thyroid was full, the fulness being due to a moderate enlargement of the gland with a small nodule in the isthmus about 2.5 cm. in diameter.

The lungs were clear on percussion and auscultation. The cardiac dulness was not increased. The heart sounds were clear. The pulse was 84 and regular; the radial arteries were thickened. The blood pressure was 125 systolic, 75 diastolic.

The abdominal aorta beat forcibly. On deep inspiration the edge of the liver was palpable about three fingerbreadths beneath the right costal margin in the parasternal line. Here, there was considerable tenderness. The right kidney could be felt on deep inspiration. The spleen was not palpable.

The patellar reflexes were extremely active. There was no tremor. There was no general glandular enlargement.

Laboratory Examinations.—Hemoglobin in the blood totaled 70 per cent.; red blood cells, 4,032,000; color index, 0.8; white blood cells, 6,900. The differential count was: polymorphonuclears, 59 per cent.; small lymphocytes, 28 per cent.; large lymphocytes, 4.5 per cent.; large mononuclears, 2 per cent.; transitionals, 4 per cent.; eosinophils, 1.5 per cent.; basophils, 0.5 per cent., and unclassified, 0.5 per cent. The Wassermann reaction was negative. The blood chemistry was: sugar, 90 mg. per cent.; urea nitrogen, 11.2 mg. per cent.; urea, 23.96 mg. per cent., and uric acid, 4.4 mg. per cent. The urine was amber, clear and acid; the specific gravity was 1.016; there was a trace of albumin but no sugar; microscopically there were large numbers of white blood cells but no casts. The basal metabolic rate was —9 per cent.

THE PATHOLOGY OF JOINT TUBERCULOSIS IN ITS EARLIER STAGES*

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Although a great deal has been written on the subject, much doubt still appears to remain as to the manner in which tuberculosis begins in joints. The consensus of the statements in the more recent text-books is that the disease starts in the bone ends, spreading thence into the joints, and that primary synovial tuberculosis is a rarity, if indeed it occurs at all. That this uncertainty or difference of opinion should exist in regard to a disease that has been studied so thoroughly is not surprising when it is considered that in the past the opportunities to see specimens at an early stage of the process have been extremely few. It would be difficult by examining the ruins of a burned house to determine in what part the fire started. The purpose in bringing up this subject again is to present the findings in a series of early cases; the routine method of dealing with this disease at the New York Orthopaedic Dispensary and Hospital has made available an unusual number.

Basing their opinions on both pathologic findings in patients and experiments on animals, Virchow,[1] Volkmann,[2] Koenig,[3] Hildebrand,[4] Krause,[5] Cheyne,[6] Fraser[7] and others described two types of joint tuberculosis, one in which the synovial membrane was involved primarily, and one in which the bone was first affected. Hildebrand[4] said that the primary synovial form is more common but that certain joints are exceptions to this rule, the elbow and hip, in his opinion, being usually the site of primary bone lesions, whereas the knee usually is affected first in the synovial membrane. He believed that the manner of onset varied according to the age of the patient but quoted Koenig and Volkmann as having directly opposed opinions about this. Hildebrand also spoke of the difficulty or impossibility of determining the mode of onset in many cases because they were not seen sufficiently early.

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* From the clinic of the New York Orthopaedic Dispensary and Hospital.

1. Virchow: Virchows Arch. f. path. Anat. **4**.
2. Volkmann: Krankheiten der Bewegungsorgane, Chirurgie Pitha-Billroth, 1865.
3. Koenig: Tuberculose der Knochen und Gelenke, 1884.
4. Hildebrand: Koenig's Lehrbuch der Chirurgie **4**:767, 1909.
5. Krause: Tuberculosis of Bones and Joints, Wood's Medical and Surgical Monographs, 1891.
6. Cheyne, W. W.: Tuberculous Disease of Bones and Joints: Its Pathology, Symptoms and Treatment, Ed. 2, 1911.
7. Fraser, J.: Tuberculosis of the Bones and Joints in Children, 1913.

Many animal experiments have been performed in an effort to throw light on this question but those of Krause [5] seem the most interesting and suggestive. He inoculated both rabbits and guinea-pigs, the former intravenously, the latter subcutaneously, with pure cultures of tubercle bacilli, and then directly, or a short time thereafter, traumatized various

Fig. 1 (Case 1).—Articular cartilage of femur and tibia with fat pad and a large part of the synovial membrane; synovial tuberculosis of knee.

joints, spraining some and dislocating others. With a single exception no joint that was not injured developed tuberculosis. All fractures healed without infection and only one dislocated joint was involved. It was the lesser degrees of injury that were followed by development of the disease. Among seventy-two sprained joints twenty-nine became

tuberculous. In all of these the synovial membrane was involved and in the majority the bone was not. In the few cases in which foci were found in the epiphyses, these were small and scattered and had no causative relation to the lesions in the synovial membrane. In three animals, however, large tuberculous foci were found in the epiphyses.

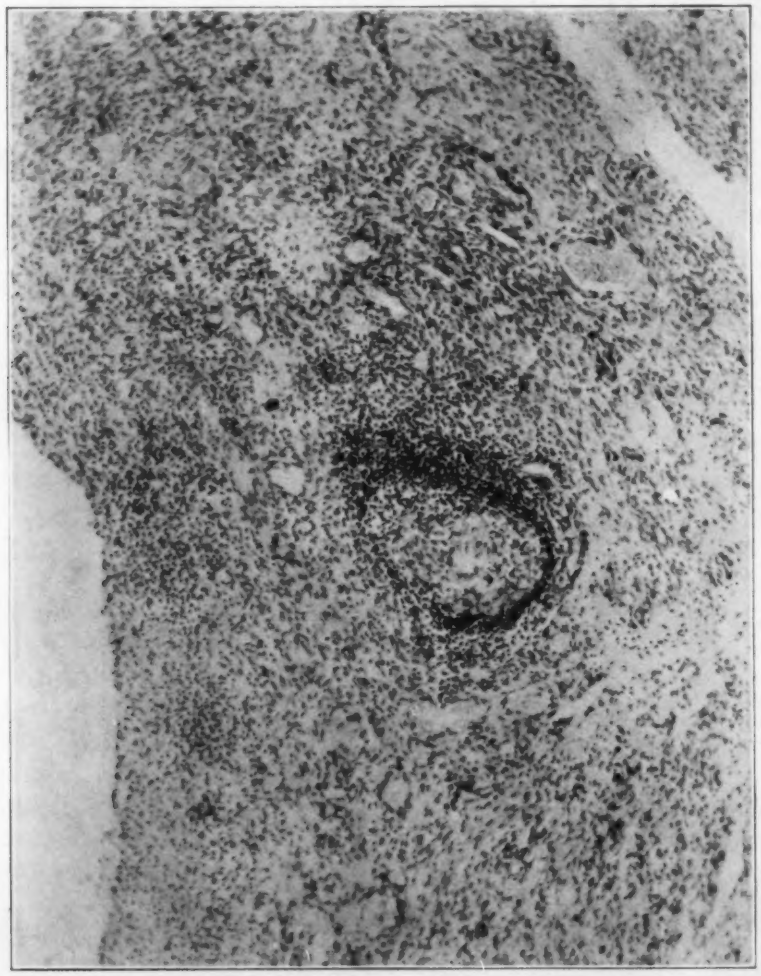

Fig. 2 (Case 1).—Tubercle in subsynovial tissue; synovial tuberculosis of knee.

In two of these the synovial membrane was intact. In the third it was tuberculous, but it was difficult to say whether this had happened simultaneously with or secondary to the bone lesion. In many cases, including those in which the joints themselves were not involved, scattered tubercles were found throughout the diaphyseal portions of the long bones, but it must be remembered that these animals were affected with a widespread miliary tuberculosis.

Nichols [8] wrote a paper in 1898 which has had great influence in shaping opinion on this subject in this country and which generally has been accepted as authoritative. He described his findings in the examination of 120 specimens obtained at necropsy and from amputations and joint resections. In every case the bone was involved. "In four

Fig. 3 (Case 4).—Articular cartilage of femur and tibia with some of the synovial membrane; synovial tuberculosis of knee of four years' duration.

cases after amputation the joint was examined carefully without finding any connection with the bone focus. In every case when the bone was opened an extensive area of caseation was found in the bones." He

8. Nichols, E. H.: Tuberculosis of Bones and Joints, Tr. Am. Orthopaedic A. **11**:353, 1898.

believed that "primary synovial tuberculosis is exceedingly uncommon, that examination at the time of operation is of no value, and that no case should be considered as primarily synovial, unless each and every bone entering into a joint is sawed into thin sections, not over 1 cm. in thickness, and carefully examined." He thought that this view was supported theoretically by the fact that tuberculosis always starts as a focal disease and spreads peripherally. Therefore, the disease in the synovial membrane should not be widespread as it usually is.

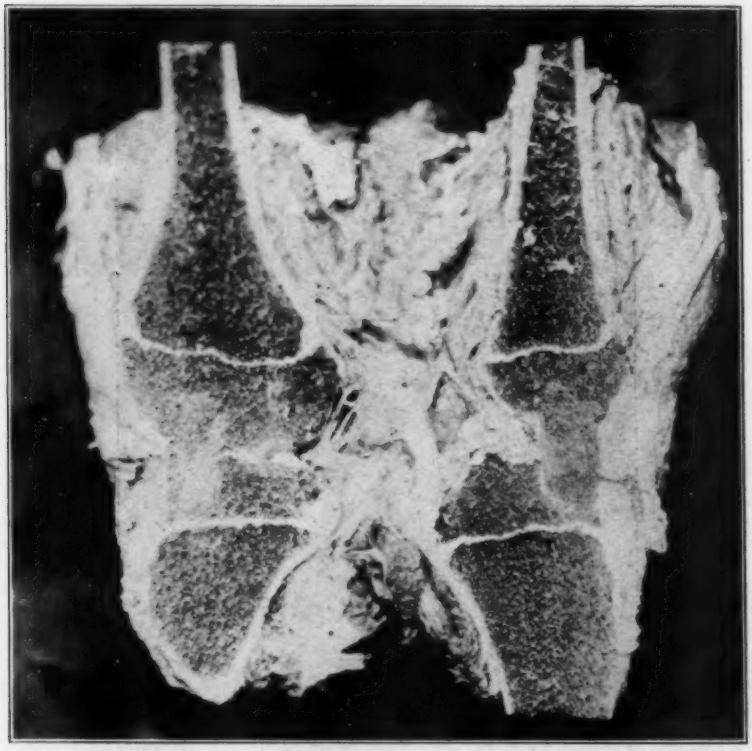

Fig. 4 (Case 10).—Knee joint firmly fixed surgically five months after operation; no involvement of bone.

These conclusions received support in an article by Allison [9] in which he described fifty specimens of tuberculous joints and bones obtained at operation. In all of them the bone was involved and in forty-one the joint as well was affected. Although admitting that he was not sure in all of these cases in what tissue the primary infection took place, he was certain that in all of them the bone became the chief seat of the infection. No evidence was found of an instance of pure

9. Allison, N.: Tuberculosis of Bone, Arch. Surg. **3**:593-626 (May) 1921.

synovial tuberculosis. He stated that he was in accord with Nichols that the disease is primarily one of bone. Allison does not give the duration of symptoms before operation in most of his cases but it seems evident from the descriptions that they were not early ones.

Fig. 5.—Tubercles in hypertrophied synovial villi from a case of tuberculosis of the hip.

There is no question of the accuracy and thoroughness of these investigations but there does seem sufficient ground to question the conclusions that were drawn, for the reason that the material selected was that from bones and joints in which a process of long duration had caused much destruction and, in most cases, must have obliterated all evidence of how it began.

In a study of the material in William C. Clarke's laboratory at Columbia University College of Physicians and Surgeons, Ely [10] found that of thirty-four specimens, four showed unmistakable evidence that the disease began in the synovial membrane, in seven the disease was

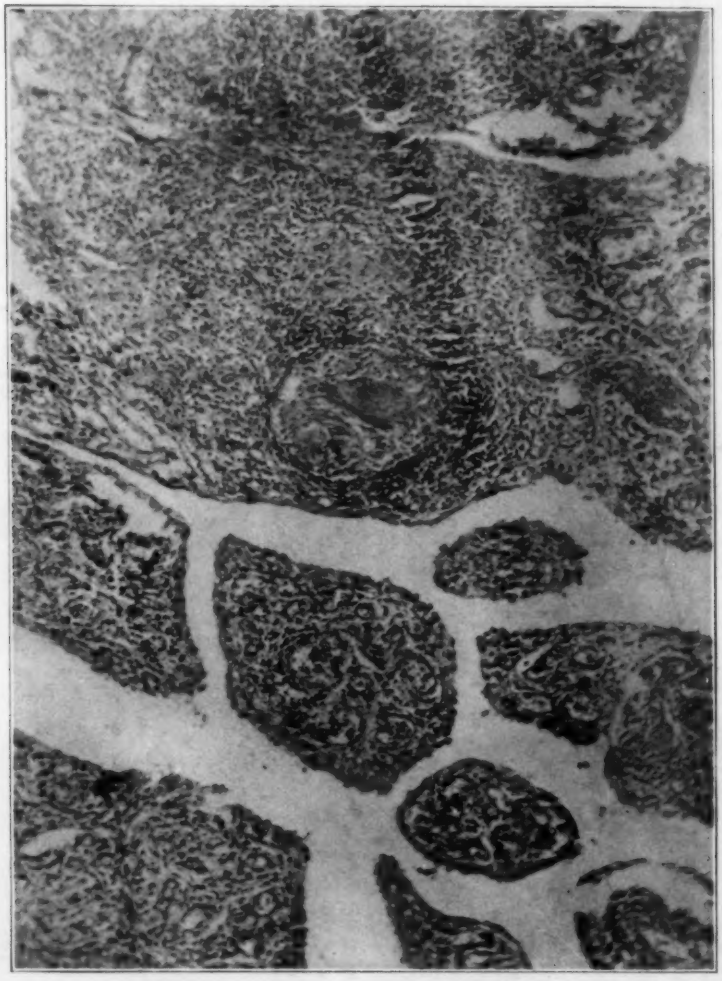

Fig. 6 (Case 13).—Synovial tuberculosis of knee.

primary in the bone, and in the remainder the manner of onset could not be determined. Clarke is convinced that in many cases, especially in the knee joint, tuberculosis starts in the synovial membrane. He calls attention to the analogy between this and tuberculosis of the

10. Ely, L. W.: Joint Tuberculosis with Special Reference to Its Pathology, M. Rec. **76**:551-554 (Oct. 2) 1909.

synovial membrane of the tendon sheaths, which is anatomically the same as that of joints.

Rogers [11] pointed out in 1922 that at the Massachusetts General Hospital, in a series of cases of exploratory operations in early cases

Fig. 7 (Case 13).—Articular cartilage covered with thick layer of fibrous tissue near the surface of which is a tubercle.

of tuberculosis of the knee and in one hip, a number were found with involvement of the synovial membrane but with no bone involvement. Since in these cases treatment consisted in injection of iodoform with-

11. Rogers, M. H.: Pathology of Tuberculosis of Joints, J. Bone & Joint Surg. 4:679 (Oct.) 1922.

out further operation, no opportunity was had to inspect the joint thoroughly. This led to the criticism that the conclusions were based on insufficient evidence.

For several years it has been the routine practice in Hibbs' Clinic, the New York Orthopaedic Dispensary and Hospital, to make abso-

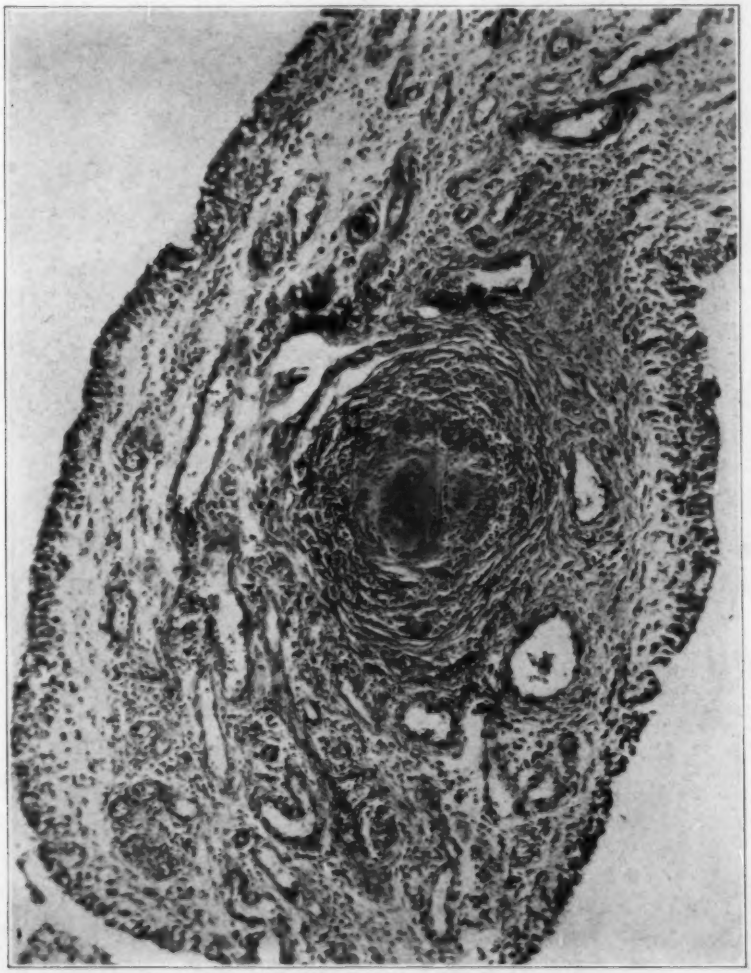

Fig. 8 (Case 15).—Large villus with tubercle in its center in synovial tuberculosis of knee.

lutely certain of the diagnosis in every early case suspected of being tuberculosis of a joint. This has been done by guinea-pig inoculation or, when that failed, by exploratory operation.[12] When the diagnosis is

12. Smith, A. D.: The Early Diagnosis of Joint Tuberculosis, J. A. M. A. **83**:1569-1573 (Nov. 15) 1924.

established an arthrodesis is performed because of the uniformly bad results from conservative treatment. This has afforded an unusual opportunity to study a group of cases in which the process was still sufficiently early to make it possible to determine where it began. No

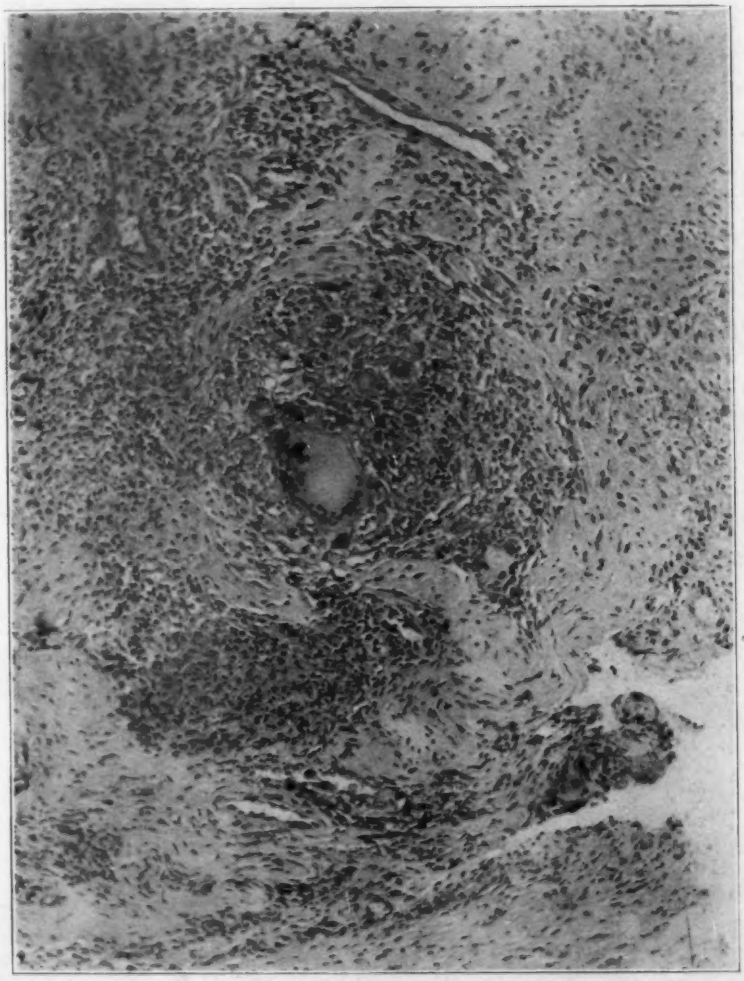

Fig. 9 (Case 9).—Section of knee joint in synovial tuberculosis of two years' duration.

case has been included in which the operative procedure did not give ample opportunity to examine the bone as well as the joint. In surgical fixation of the knees the Hibbs [13] method was used. This consists in

13. Hibbs, R. A.: Tuberculosis of the Knee Joint in the Adult in Which Operations Were Done Eliminating Motion by Producing Fusion of the Femur and Tibia, New York M. J. **105**:922 (May 19) 1917.

the removal of the articular cartilages of the femur, tibia and patella, after which a notch is made in the femoral and tibial epiphyses. This makes it possible to examine the interior of the bone as well as its surface.

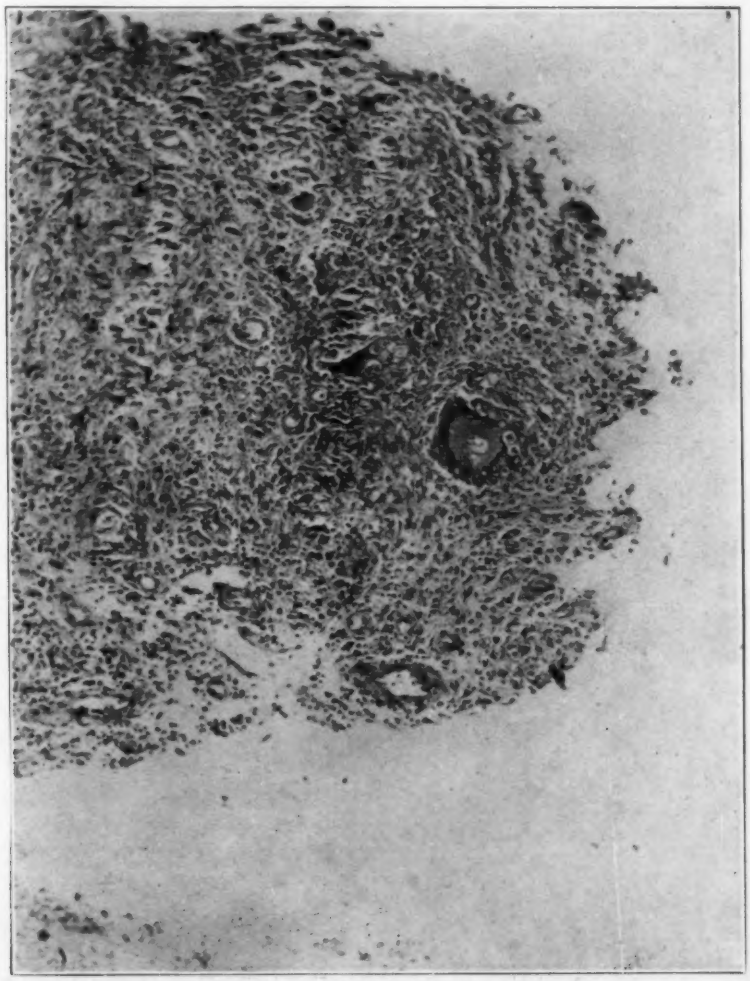

Fig. 10 (Case 12).—Tuberculosis of synovial membrane in metatarsocuneiform joint.

The series consists of twenty-three cases, in twenty of which either the bone of the synovial membrane alone was involved, and in three of which both were affected, but in which the rapidity of the process made it seem probable that the bone was involved from the start. A number of cases in which the extensive involvement of the synovial membrane, and the comparatively slight involvement of the bone adjacent to the

articular surface, made it seem probable that the synovia was the starting point were not included because of the impossibility of being certain about this point. In all of the cases the diagnosis was proved either by microscopic examination or by guinea-pig inoculation.

Fig. 11 (Case 11).—Section of synovial membrane from knee joint; the bone was not diseased.

GROUP 1

The first group of cases comprises those in which the synovial membrane was involved and in which the bone was not. They were seventeen in number, the patients varying in age from 6 to 32 years and averaging 14 years. Eight were 10 years of age or less and four were adults from 23 to 32. In fifteen of these cases the knee

joint was affected, in one the ankle and in one the metatarsocuneiform joint. The average duration of symptoms from onset to time of operation was one year and eight months. In one instance it was five years, in another four years and four months, and in a third four years.[14] During this period the disease remained in the synovial membrane without spreading to the bone. This is in contrast to the cases with primary bone involvement in which the course was more rapid. The common, slowly progressing, insidious case of joint tuberculosis, which we are accustomed to think typical, is, I believe, in most all instances this synovial form. Examples of this are the following:

REPORT OF CASES

Case 4.—A. D., a boy, aged 9 years, with tuberculosis of the right knee, was admitted to the dispensary, Dec. 19, 1922. He had had pain and swelling in the right knee for two years. On admission there was swelling of the knee, atrophy of the thigh and calf, limited motion, muscle spasm and decalcification of the bone. Roentgen-ray examination showed a thin joint space and decalcification of bone. There was no cavitation. The Wassermann reaction was negative. The human Pirquet test was negative; the bovine, negative. Leukocytes totaled 10,500; polymorphonuclears, 64 per cent. A brace was applied and the patient was sent to the country branch of the hospital. Following removal of the brace in 1924, motion diminished and spasm increased. An exploratory operation was performed, Nov. 21, 1924. The synovia was dark, congested and edematous. A pannus of vascular tissue was found invading the articular cartilage at its margin, but the cartilage was not eroded. Many fibrous adhesions were present. The pathologic report was tuberculosis of the synovial membrane. Knee fusion was done by Hibbs' technic, Dec. 30, 1924. The process was most extensive on the inner side of the joint although the entire joint space was involved. Laterally, a thin, fibrous pannus extended over the entire surface of the cartilages, while medially dense adhesions bound the synovial tissue to the articular surfaces. In these adhesions were degenerated areas, caseous and gelatinous. The suprapatellar bursa was obliterated. At no place was there any evidence of involvement of cartilage or bone.

Case 10.—E. K., a boy, aged 13 years, with tuberculosis of the right knee, was admitted to the dispensary, Sept. 5, 1922. He was a typical cretin, with the physical development of a boy 8 or 9 and subnormal mentality. For eighteen months he had had swelling and stiffness of the right knee and had worn a plaster cast; but had had no treatment for six months. On admission there was marked swelling of the joint, limitation of motion and spasm, with atrophy of the leg and thigh. Roentgen-ray examination showed a thin joint space, decalcification of the epiphyses, and marked effusion. The Wassermann reaction was negative. The Pirquet test was positive.

September 21, cloudy yellow fluid from the knee was injected into a guinea-pig. November 22, when the pig was killed, it was found negative for tuberculosis.

An exploratory operation was performed, Sept. 29, 1922. A large amount of clear yellow fluid was found in the joint. The synovial membrane was greatly

14. It will thus be seen that the term early, as applied to these cases, is relative only. It is expected that as more accurate methods of diagnosis are applied such cases will be detected and treated much sooner.

thickened and deep red. A pannus of vascular tissue encroached on the margins of the articular cartilage of the femur. There was an erosion about 5 mm. in diameter over the lateral femoral condyle of the femur but the exposed bone appeared normal. The pathologic report was tuberculosis of the synovial membrane. Knee fusion was done by Hibbs' technic, Oct. 27, 1922. Extensive involvement of the synovial membrane was found but no evidence of disease of the

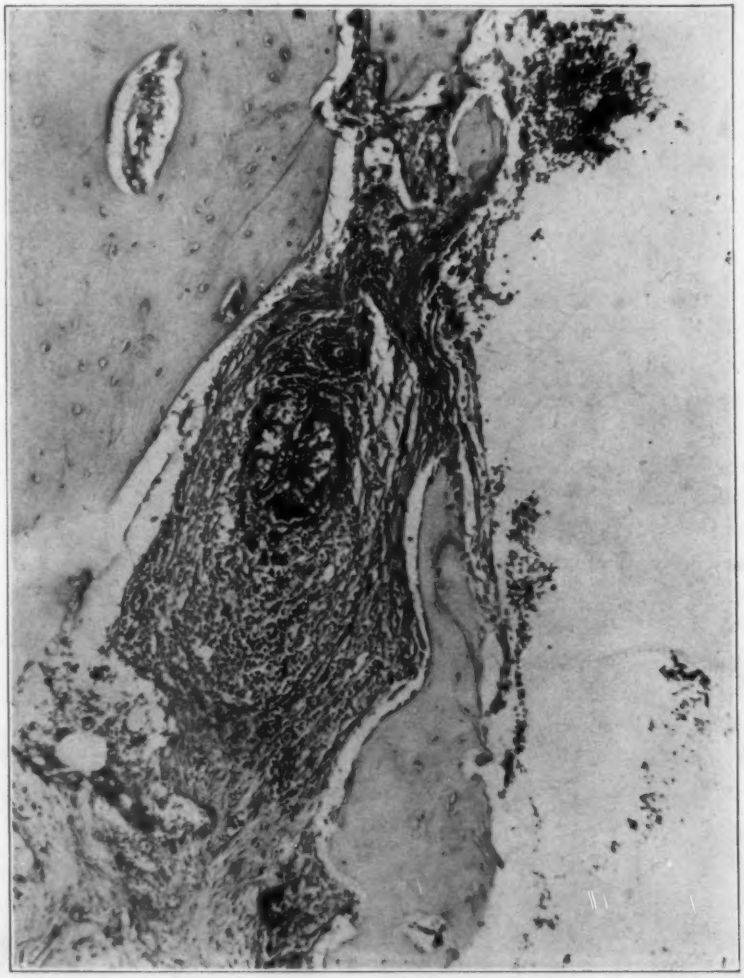

Fig. 12 (Case 19).—Tuberculosis of greater trochanter of femur.

cartilage or bone. In March, 1923, five months after operation, the patient died. Necropsy revealed tuberculosis of the meninges and extensive adhesions in the left pleural cavity. The right knee joint, with the adjacent ends of the tibia and femur, was removed. The specimen was sawn in two in a midsaggital plane, and a complete section about 8 mm. in thickness was taken from the center. The femur was quite firmly united to the tibia. The patella was morticed in between the two bones and some new bone had formed in front of it. The posterior part

of the femoral and tibial epiphysis was soft but did not appear definitely pathologic (Fig. 4). Sections were made of the entire joint, including the epiphyseal cartilage of the femur and tibia and the adjacent portions of the diaphyses. No tuberculosis was found except at the line of junction of the femur with the tibia, where a few scattered tubercles were encountered.

The usual picture in the earliest of these cases was that of a thickened, deep red, vascular synovial membrane, limited to the region of the fat pad, the recesses at the sides of the joint, around the cruciate ligaments and the suprapatellar bursa. In some instances small, whitish specks, probably miliary tubercles, could be seen with the naked eye. Except for a thin, vascular pannus on the margins of the femur, the articular cartilages were smooth, glistening and unchanged in texture. The underlying bone was intact and showed no evidence of disease. From this the picture showed various progressive changes to that in which the entire joint space was obliterated by adhesions of fibrous and granulation tissue, in which were masses of caseous and gelatinous material. The cartilage in these more advanced cases was completely covered with granulation tissue and was somewhat worn in places but not perforated. Still, the bone of the femoral and tibial epiphyses and the patella showed no evidence of disease.

In the earliest cases the sections of tissue showed hypertrophied synovial villi, often with a margin consisting of several layers of cells instead of one. The vessels were engorged and the tissue spaces were infiltrated with many lymphocytes, here and there in groups. A further search revealed groups of large epithelioid cells with vesicular nuclei surrounded by a fringe of lymphocytes. These resembled tubercles in many respects but lacked the typical giant cells. Always one or more of these could be found, however, if the pains were taken. In most of the cases in which they were sought, tubercle bacilli were found, but in small numbers. In the older cases areas of fibrous tissue with no tubercles alternated with amorphous, degenerated areas around which in places were many tubercles.

GROUP 2

In Group 2 are included those cases in which there was involvement of bone without that of a joint, three in number. They were in (1) an infant of 16 months, with a lesion in the lower end of the femur; (2) a child of 3 years, with a focus in the lower end of the tibia, and (3) a man, aged 25, with a small focus in the greater trochanter. The average duration of symptoms before operation in these cases was eight months. In the case of the infant it was only one month, which makes it probable that the process was well developed before the parents noticed it; but the man had well defined symptoms and roentgen-ray evidence of the lesion in the trochanter five months before he was operated on. In the case in the lower end of the femur and in that in the

lower end of the tibia, the lesion most probably started on the diaphyseal side of the epiphyseal line. In each instance it had extended through the epiphyseal cartilage and had invaded the epiphysis, but by far the greater extent of the focus was on the diaphyseal side. The knee and

Fig. 13 (Case 20).—Tuberculous lesion in metaphysis of femur; the joint was not involved.

ankle joints were not involved, but had the process in the lower end of the tibia gone much longer it must soon have invaded the joint.

In each instance the cavity was filled with a viscid, gelatinous granulation tissue. The bony walls were often soft and not sharply limited. In the lower end of the femur there was a subperiosteal proliferation of bone more suggestive of a staphylococcus than of a tuberculous infection.

Microscopic examination showed tubercles in the marrow spaces. This type of lesion is infrequent but certainly not rare.

GROUP 3

In Group 3 are included three cases in which both bone and synovial membrane were involved, and about which, therefore, no definite state-

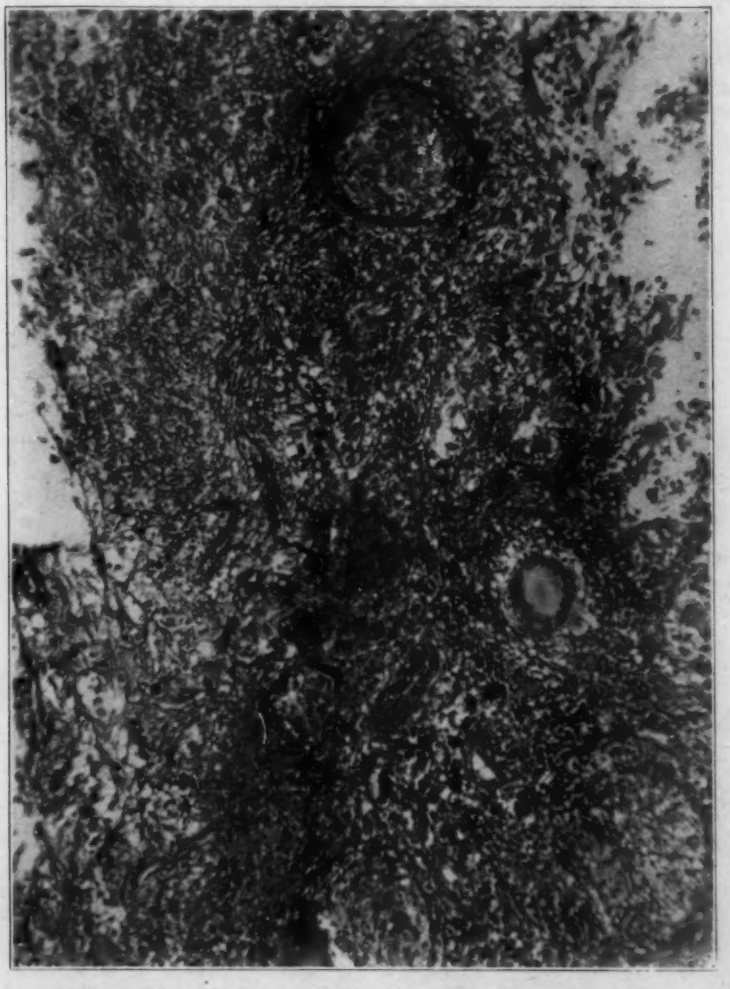

Fig. 14 (Case 20).—Granulation tissue from cavity in femur.

ment can be made as to where the disease started. All are early cases, however, and in each an extensive bone involvement makes it seem probable either that the bone was the primary seat of the lesion, from which it spread rapidly to the synovial membrane, or that the bone and synovial membrane were infected simultaneously, as they were in some

of Krause's guinea-pigs and rabbits. The average age of these patients was 4 years. The regions involved were: the neck of the femur and the hip joint; the astragalus and the ankle; and the upper end of the tibia and the knee joint. The average duration before operation was seven months. In the hip it was four months, although the patient was brought to the clinic one month after the onset of symptoms and then had a very acute joint with extensive changes in the neck of the femur, as shown by roentgen-ray examination. The ankle case gave a definite history of onset five months before admission. The first symptoms in the knee were somewhat indefinite, because the child had had pain in both knees for about a year. The following is a characteristic case of this kind:

CASE 22.—H. D., a girl, aged 3 years, with tuberculosis of the left ankle and astragalus, was admitted to the hospital, Feb. 10, 1925. She had had pain and swelling of the left ankle for about five months. The onset was sudden, the patient waking up one morning complaining of pain in the left ankle. Since then she had walked with a marked limp. She was admitted to the Presbyterian Hospital, Feb. 3, 1925, and transferred to the New York Orthopaedic Hospital, February 10. The left ankle was swollen, with doubtful fluctuation, slightly warmer than the right and not tender. There was scarcely any limitation of motion or muscle spasm. Roentgen-ray examination showed irregular density and loss of substance in the proximal half of the astragalus. An effusion was present in the ankle joint. The Mantaux test was positive; the Wassermann reaction, negative. Leukocytes totaled 5,600; polymorphonuclears, 60 per cent. The temperature was from 100 to 101 degrees.

February 3, 3 c.c. of sanguinoserous fluid was aspirated from the ankle, cultured and inoculated in a guinea-pig; the culture was sterile.

February 20, an exploratory operation was performed. The ankle joint was distended with thick, creamy pus. The synovial membrane was greatly thickened and the cartilage over the superior surface of the astragalus was partly detached. The bone was eroded. Cultures were sterile.

The pathologic report of the tissue was that the synovial fringes were packed with small round cells and thickly studded with typical miliary tubercles. The giant cells were unusually large and well formed. The process seemed very active and rapidly progressing. March 9, the ankle joint was fixed surgically by removing the articular cartilage from the upper facet of the astragalus and the lower end of the tibia.

In the three years from March, 1922, to March, 1925, 190 operations were performed on tuberculous joints at the New York Orthopaedic Hospital, exclusive of those on the spine. The twenty-three cases forming the material for this study are the only ones of that number from which a conclusion could be drawn as to the manner of onset. Each case was proved definitely to be tuberculosis and in each the lesion was clean cut and comparatively early.

Although the study is based on clinical data and operative findings as well as the pathologic material, no case was accepted in which it was felt that the operative procedure did not give opportunity for a thorough examination of the bone as well as of the joint itself.

In analyzing the cases the first noteworthy fact is that in the large majority the synovial membrane alone was involved. The series included more knee joints than any other and it may be that this proportion would not hold good in some of the other articulations. We have been impressed, however, as the number of early cases accumu-

Fig. 15 (Case 18).—Tuberculous lesion which started in metaphysis of lower end of tibia and which did not involve the joint at time of first operation.

lated, with the large proportion that started in the synovial membrane, and we are inclined to believe that this is the way in which the disease usually begins in joints. An interesting feature of these synovial cases was their slow progress and the long period of time during which the lesion was confined to the synovial membrane.

In the six cases in which the bone was involved the history was of much shorter duration. In several the period was so short and the onset so definite that it was thought probable that the condition was a pyogenic infection. If we allow for inaccuracy of observation on the part of the patient or the parents, it seems quite certain that the course of the disease was much more rapid in these than in the synovial cases. Another point about these cases was the unmistakable roentgenographic evidence of a bone lesion as soon as the patient was seen. Although it is commonly believed that the disease starts in the epiphyses and then spreads to the synovial membrane, no case was found in which the lesion was confined to the epiphysis or in which it seemed probable that it had started there.

CONCLUSIONS

1. Of a series of twenty-three cases of joint tuberculosis in which it could be determined where the disease began, seventeen were primary synovial and three primary bone lesions. In three other cases the disease probably started in the bone.

2. It is believed that the disease starts in the synovial membrane in the majority of cases in the knee and probably in other joints as well.

3. The course of the disease was slower and more insidious in the synovial cases than in those with bone lesions.

4. When a bone lesion was present it was easily recognizable by roentgen-ray examination.

5. No instance was found in which the disease was confined to an epiphysis, although there were three in which it started in the metaphyses.

6. Conclusions as to what tissue is first diseased in joint tuberculosis based on much of the material studied in the past are open to question because of the advanced stage of the cases from which the material was obtained.

THE EFFECT OF THE SYMPATHETIC NERVOUS SYSTEM ON THE PERIPHERAL VASCULAR SYSTEM

AN EXPERIMENTAL STUDY *

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AND

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PHILADELPHIA

Following the impetus given periarterial sympathectomy by Leriche [1] in 1913, when he first began to use the procedure extensively, the literature has become progressively more abundant with case reports and speculations as to its benefits. Leriche, however, can scarcely be given credit for originating the procedure, as Jaboulay in 1889 performed the identical operation but did not report it. Jaboulay in turn had obtained the idea from the well known work of Bernard,[2] who showed the influence of the sympathetic nervous system on the circulation of blood in the ear of a rabbit. Since 1914 there has been so much written on the subject that even the occasional reader is well informed concerning the diversified pathologic conditions for which it has been advocated, either as a cure or as a form of symptomatic relief. It has been used for trophic neuroses, scleroderma, acro-asphyxia, acroparasthesias, trophic ulcers, Raynaud's disease, causalgia, varicose ulcers, tuberculous and other diseases of the joints, senile gangrene, arteriosclerotic gangrene and endarteritis obliterans (Buerger's disease) with varying success.

What first impresses the scientific student in reading the literature is the total absence of basic experimental work to explain the apparent beneficial results. Nothing has been added to the as yet unconfirmed statement of Leriche in his original article that in man the predominating vasomotor influences are carried by the perivascular sympathetic nerves. It was to determine something definite concerning this basic hypothesis, on which the whole theory of periarterial sympathectomy rests, that we did the experimental work contained in this article. We began the work with a totally unbiased opinion, without hope of either refuting or corroborating the clinical deductions, except so far as actual

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* From the department of surgery, University of Pennsylvania School of Medicine.

1. Leriche, R.: Lyon chir. **10**:378, 1913.

2. Bernard, Claude: Leçons sur la Physiologic et la Pathologie du Systeme nerveux, **2**:508, 1868.

scientific results should dictate. That we should have digressed from our original plan was due only to logical deductions.

Impressed by the work of Potts,[3] who showed by histologic examination that local damage to a vessel injures the perivascular plexus only at that point, we decided to observe the effect of such damage on the vessels distal to the injury in the living animal. Ten cats were selected and a periarterial sympathectomy performed on the right femoral artery of each. A control incision with isolation of the artery was performed in the opposite leg in five of these animals. The arteries were exposed well up in the thigh and about 1½ inches (3.7 cm.) of the adventitia completely "stripped."

The criticism so often made that the small size of the vessels in animals makes complete denudation impossible would seem to be unwarranted, because in animals consideration of irreparable injury to the vessel wall is of little importance, as compared to the care that must be exercised in operating on the human being. It would seem, therefore, that more, instead of less, complete denudation could be performed in the animal. Although histologic examination of the excised tissue was not made, we felt reasonably certain that all of the adventitia and probably part of the media had been removed. In fact several animals were discarded because the vessel ruptured during the procedure.

In attempting to observe the results of the operation we soon recognized the impracticability of using platysmagraphic tracings of blood pressure variations. We then attempted to measure indirectly the extent of vasodilatation by measuring the water displacement of the leg. This also was found to be inaccurate. Throughout our experiments, therefore, we have used changes in temperature as the criterion by which results were measured. As only gross changes are of any value this appeared to offer a satisfactory method. An ordinary centigrade thermometer was used and the readings made by inserting the bulb beneath the web of the paws. Control observations showed only minor differences of temperature between the feet of the normal animal, although it was usually found that the temperature of the hind feet was about 1 degree higher than that of the front ones. We also found in our control animals that wide variations occurred in the same leg on different days even when the surrounding temperature was constant. Temperature observations were made on the first, second, fourth, sixth and tenth days and on each succeeding fifth day thereafter.

Of the ten cats operated on, only one showed an appreciable temperature change. In this animal on the first postoperative day the leg showed a hyperthermia of 2 degrees which persisted for four days. The

3. Potts, L. N.: Anat. Anz. **47**:138, 1914.

remaining nine animals showed no change of temperature. Satisfied that in the cat periarterial sympathectomy produces little, if any, change in the state of the peripheral circulation, five dogs were then selected and the same operation performed on them. In one of the dogs a variation of 1 degree was found when observed on the first and second postoperative days, as is shown in Table 1. No change was noted in the remaining four dogs at any time.

These results would certainly appear to indicate that at least in dogs and cats vasomotor impulses must have an extravascular course. They are particularly interesting in view of the findings of Lehman,[4] who after following the same technic obtained results very similar to ours. Of other experimental work, that of Elving[5] is worthy of mention. By direct examination of the capillaries following periarterial sympathectomy he observed improvement of the circulation in four instances, decline in two, and no change in six. These results, however, can well be explained by the work of Sherrington,[6] who has demonstrated very conclusively that freshly excised arteries exhibit different diameters under the same wall tension when there is absolutely no sympathetic connection.

TABLE 1.—*Temperature Readings Following Periarterial Sympathectomy*

	Before Operation	First Day	Second Day	Fourth Day	Sixth Day	Tenth Day
Right hind foot	23	24	24	21	22	22
Left hind foot	23	23	23	21	22	22
Right front foot	23	23	22	21	21	21
Left front foot	23	23	22	21	21	21
Room	22	22	22	20	21	22

Thus far we were forced to conclude that our work was merely a confirmation of the teaching of Langley,[7] who has shown so clearly that practically all vasomotor impulses leave the cord through the white rami communicantes as preganglionic impulses to reach the sympathetic chain. The impulses then return to the cord through the gray rami of the same spinal segments, later to be carried by the spinal nerves, which innervate the vessels at different levels. Accepting this theory we then decided to attempt interruption of the impulse in the spinal nerves. Because of its extensive distribution the sciatic nerve was selected.

The first animal operated on was a cat on which previous periarterial sympathectomy had failed to produce a change of temperature. The nerve was isolated and the sheath injected over an area of 1 inch

4. Lehman, E. P.: Ann. Surg. **11**:30 (Jan.) 1923.

5. Elving: Finska Lakeresalls kopetos, Helsingfors, July-August, 1923.

6. Sherrington: Brain **38**:224, 1915.

7. Langley, J. N.: The Sympathetic Nervous System, Shafer's Textbook of Physiology **2**:616, 1900.

(2.5 cm.) with 35 per cent. alcohol solution. An immediate typical sciatic muscular paralysis was produced with an astonishing hyperthermia, amounting on the first day to 5 degrees C. and continuing with some variation to the sixtieth day, when the last reading was made. The complete muscular paralysis continued for several days, then gradually subsided until the fortieth day, when it entirely disappeared. The complete record is shown in Table 2.

Following this observation alcoholic injection was performed on several cats that had not had a previous decortication performed. In all these animals, as well as in two others in which decortication had

TABLE 2.—*Temperature Readings in Cat 1*

	Right Femoral Sympathectomy					Right Sciatic Injection (35 Per Cent. Solution)								
	Before Operation	1st Day	2d Day	4th Day	6th Day	7th Day	8th Day	13th Day	15th Day	20th Day	25th Day	30th Day	40th Day	45th Day
Right hind foot.	35	31	31	29	29	36	35	35	33	28	33	33	34	33.5
Left hind foot..	35	30.5	31	28.5	29	31	28	33	28	23	30	29	27	28.5

TABLE 3.—*Temperature Readings in Dogs 1 and 2*

Dog 1.—Right Sciatic Injection (35 Per Cent. Solution)

	Before Operation	1st Day	2d Day	4th Day	6th Day	10th Day	15th Day	20th Day	25th Day	30th Day	35th Day	50th Day	60th Day
Right hind foot.....	27	34	35	31	33.5	30.5	34	34	31	33	31.5	32	35
Left hind foot.....	27	28	33	26	29.5	27.5	32	31	30	31	28	29	34

Complete paralysis; partial recovery on fifteenth day; complete recovery on thirtieth day.

Dog 2.—Right Sciatic Injection (35 Per Cent. Solution)

	Before Operation	1st Day	2d Day	4th Day	6th Day	10th Day	15th Day	20th Day	25th Day	30th Day	35th Day	50th Day
Right hind foot.....	28	35	35	35	33	33	25	26	29	28	23	23
Left hind foot.....	28	29	28	28	27	30	25	25	28	27	24.5	23

Complete paralysis; partial recovery on fiftieth day (toe drop at times).

been tried, there was a constant hyperthermia of the operated leg of 2 or more degrees, lasting from six to fifteen days. In none, however, was a lasting result obtained similar to the one given in Table 2.

It was then decided to try the same procedure on dogs. Four animals were injected. Two of these died within the first ten days; the others are still living. Their records are shown in Table 3.

It will be seen from Table 3 that after the injection an immediate hyperthermia was produced in the foot of the leg operated on, varying during the succeeding fifteen days between 2 and 7 degrees; that there was a gradual return toward the normal, and that in Dog 2 the temperature readings after coinciding on one day again slightly diverged.

Two dogs on which a previous periarterial sympathectomy had failed to change the temperature readings were then subjected to an alcoholic injection with the results noted in Table 4.

Four dogs were then subjected to a combined operation; that is, periarterial sympathectomy and injection with 35 per cent. alcohol

TABLE 4.—*Temperature Readings in Dogs 3 and 4*

Dog 3

	Right Femoral Sympathectomy						Right Sciatic Injection (35 Per Cent. Solution)								
	Before Operation	1st Day	2d Day	4th Day	6th Day	10th Day	1st Day	2d Day	4th Day	6th Day	10th Day	15th Day	20th Day	25th Day	35th Day
Right hind foot	24	24	25.5	29	30	30	36.5	36	36	35	36	36	34	35	25
Left hind foot	24	25	25.5	30	30	30	30	30	30	30	30	34	32	33	32

Complete sciatic paralysis; partial recovery on 15th day, but toe drop still persisted on fiftieth day.

Dog 4

	Right Femoral Sympathectomy						Right Sciatic Injection (35 Per Cent. Solution)					
	Before Operation	1st Day	2d Day	4th Day	6th Day	10th Day	1st Day	2d Day	4th Day	6th Day	10th Day	
Right hind foot	27	28	27	28	29	28	32	33	33	32	33	Died of inanition on tenth day
Left hind foot.	27	28	27	27	29	27	27	28	27	28	29	

Complete paralysis; no recovery.

TABLE 5.—*Temperature Readings in Dogs 5 and 6*

Combined Operation; Right Femoral Sympathectomy and Right Sciatic Injection (35 Per Cent. Solution)

Dog 5

	Before Operation	1st Day	2d Day	4th Day	6th Day	10th Day	15th Day	20th Day	25th Day	30th Day	35th Day
Right hind foot	23	32	35	24	28	35	32	30	29	28	26
Left hind foot.	23	23	27	25	25	32	29	29	29	28	27

Complete paralysis; partial recovery on fifteenth day; complete recovery on thirty-fifth day.

Dog 6

	Before Operation	1st Day	2d Day	4th Day	6th Day	10th Day	15th Day	20th Day	25th Day	30th Day	35th Day
Right hind foot	28	37	36	35	35	35	34	35	32	32	27.5
Left hind foot	28	28	29	31	27	25	29	32	29	29	25

Complete paralysis; partial recovery on tenth day; complete recovery on twenty-fifth day.

solution of the sciatic nerve of the same leg on the same day. Two of the dogs died of a respiratory infection, one on the fifth day, the other on the seventh day. Both showed a very marked change of temperature but on account of incomplete observation time they have been omitted from our records. The temperature readings of the other two are shown in Table 5.

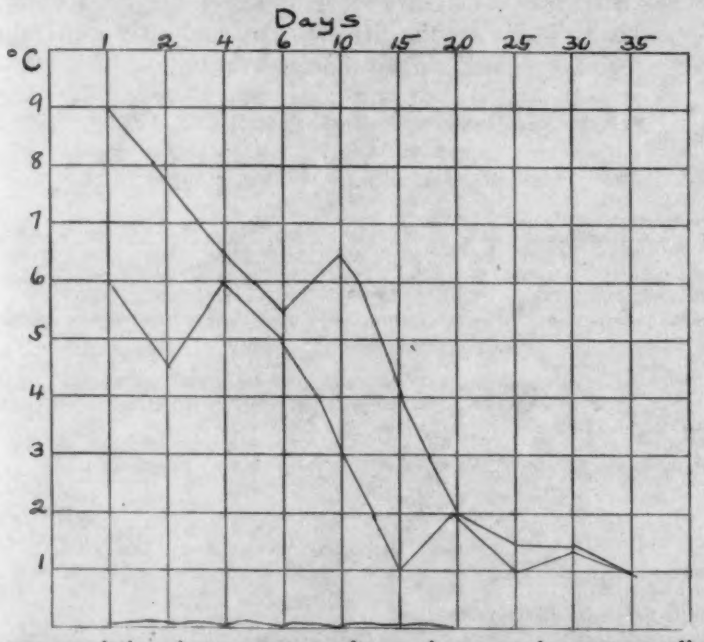
When the accompanying tables are examined collectively one is impressed with several things:

1. Alcoholic injection of the sciatic nerve in sufficient strength to cause motor paralysis also causes hyperthermia.

2. There is a gradual recovery of the motor function of the leg.

3. The hyperthermia declines, approximately, in proportion to the extent of motor recovery.

4. When the alcoholic injection follows, or is made at the same time as, a periarterial decortication, the increase of temperature is more marked than in those animals in which injection alone was performed.



Average variations in temperature after various procedures: upper line, combined operation; middle, sciatic injection; lower, periarterial sympathectomy.

The last conclusion requires some elucidation. If the average changes of temperature over a thirty-five day period are analyzed the following results are obtained:

1. Average hyperthermia following periarterial sympathectimy = Less than 0.1 degrees C.

2. Average hyperthermia following alcoholic injection of sciatic nerve = 3.12 degrees C.

3. Average hyperthermia following sciatic injection subsequent to periarterial sympathectomy = 4.54 degrees C.

4. Average hyperthermia following simultaneous sciatic injection and sympathectomy = 4.52 degrees C.

These results are shown alsc in the accompanying chart.

A glance at this chart indicates that in our animals, while the actual average temperature variations are greater in those subjected to a combined operation, the return toward the normal temperature is at about the same rate. This would appear to indicate that the combined operation blocks all vasomotor influences while paralysis of the spinal nerves alone blocks the great majority of them.

Thus far we had intentionally produced a complete motor paralysis, thus insuring complete vasomotor paralysis. Alcohol solution in 35 per cent. strength was used. It was observed that in these animals complete or partial return of motor function occurred. In fact, in only one dog that lived more than thirty-five days was the toe drop permanent. Recovery usually began on the fifteenth day and on the average was complete between the thirtieth and the fortieth day.

TABLE 6.—*Temperature Readings in Dogs 7, 8 and 9*

Right Sciatic Injection (15 Per Cent. Solution)

Dog 7

	Before Operation	1st Day	2d Day	4th Day	6th Day	10th Day	15th Day	20th Day	25th Day	30th Day
Right hind foot.....	32	33	36	36	37	35	33	31	31	32
Left hind foot.....	32	31	33	34	36	30	29	27.5	29	31

Complete paralysis; partial recovery on fifteenth day; complete recovery on thirtieth day.

Dog 8

	Before Operation	1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day	10th Day	11th Day	15th Day	20th Day	25th Day	30th Day
Right hind foot...	32	37.5	32	27	23.5	26.5	33	29	32	25	25	24	24.5	33
Left hind foot....	32	32	26	25	25	27	29	29	35	28	26	28	26	33

Paralysis, except absence of toe drop; refused to use leg for twenty days.

Dog 9

	Before Operation	1st Day	2d Day	4th Day	6th Day	10th Day	15 Day	
Right hind foot.....	30	32	36	37	34	31	34	Killed; distemper
Left hind foot.....	30	29	30	35	33	27	30	

Complete paralysis; no recovery; killed.

In view of these observations we decided to reduce the strength of the alcohol used, in an attempt to determine whether a point could be reached where vasomotor paralysis could be produced without permanent motor paralysis. Several dogs were injected with 15 per cent. alcohol solution. Many died from an epidemic of distemper. The records of the surviving ones are shown in Table 6.

It will be noticed that Dogs 7 and 9 responded to the injection in much the same way as the dogs injected with 35 per cent. alcohol solution. Dog 8, however, gave a confusing record. His paralysis, which was complete, began to improve on the fifteenth day and was complete on the thirtieth day. During the stage of complete paralysis a hyperthermia occurred in the operated leg. During the period of recovery

this condition changed to hypothermia. This reversal of temperature, which at first seems confusing, we interpreted to be due to more rapid recovery of the vasoconstrictor fibers, and therefore was probably due to peripheral vasoconstriction. This result was not unexpected. In fact, bearing in mind the statement of Gaskell [8] that vasoconstrictor fibers regenerate much sooner than do vasodilator fibers, we were surprised that we did not observe this reversal more frequently.

One dog was injected with 10 per cent. alcohol solution; the record is shown in Table 7.

Two dogs were injected with 5 per cent. alcohol solution. Their records are shown in Table 8.

TABLE 7.—*Temperature Readings in Dog 10*

Right Sciatic Injection (10 Per Cent. Solution)
Dog 10

	Before Operation	1st Day	2d Day	4th Day	6th Day	10th Day	15th Day
Right hind foot	31	35	34	32	31.5	32	34
Left hind foot	31	32	31	27	28	29	32

Complete paralysis; partial recovery on fifteenth day.

TABLE 8.—*Temperature Readings in Dogs 11 and 12*

Right Sciatic Injection (5 Per Cent. Solution)
Dog 11

	Before Operation	First Day	Second Day	Fourth Day	Sixth Day	Tenth Day
Right hind foot	31	30	30	29	26	28
Left hind foot	31	30	30	29	27	28

No paralysis.

Dog 12

	Before Operation	First Day	Second Day	Fourth Day	Sixth Day	Tenth Day
Right hind foot	32	32	31	24	23	31
Left hind foot	32	32	31	24	23	31

No paralysis.

In neither of the animals injected with 5 per cent. alcohol solution was there any motor paralysis at any time. It is interesting to note the average changes of temperature in the latter group of animals as compared to those injected with 35 per cent. alcohol solution:

Average hyperthermia in 35 per cent. solution group = 3.12 degrees C.
Average hyperthermia in 15 per cent. solution group = 3.1 degrees C.
Average hyperthermia in 10 per cent. solution group = 3.16 degrees C.
Average hyperthermia in 5 per cent. solution group = 0 degrees C.

8. Gaskell, W. H.: Involuntary Nervous System, New York, Longmans, Green & Co., 1916.

These comparisons show a uniform hyperthermia in all animals in which paralysis was produced, and have led us to conclude that vasomotor paralysis can only be secured by injecting in sufficient quantity to produce some degree of motor paralysis; and furthermore that the degree of vasomotor paralysis is not increased by injecting a more concentrated solution. The attempt to produce vasomotor paralysis by injecting in only sufficient strength to produce partial motor or sensory paralysis was unsuccessful, as it is extremely difficult to gage the extent of paralysis in the experimental animal. This is a problem that can only be solved by observations on the human. In view of the constant hyperthermia produced and the uniform recovery of function even after the injection of concentrated solutions, we believe that the procedure not only deserves a clinical trial, but also is a much more logical method of producing the results claimed by the advocates of periarterial sympathectomy.

We are well aware of many sources of error in our work. The method of measuring the degree of vasodilatation is admittedly crude, but if such an easily applied method shows marked variations, then a more accurate method of measurement would certainly be expected to show even more marked vasodilatation. It has been impossible to measure accurately the concentration or amount of alcohol injected, owing to leaking from the sheath; it has been impossible to observe the effect of producing variations in the degree of paralysis. The variations of temperature in the habitat of the animals has no doubt been of some influence. However, the experimental results obtained coincide in general with the clinical results of Taylor and Rice of Panama in 1924 (published elsewhere), except that they observed hyperthermia in some of their cases in which no paralysis was produced.

CONCLUSIONS

1. Periarterial sympathectomy in dogs and cats has uniformly failed to produce hyperthermia.

2. Alcoholic injection of the sciatic nerve in sufficient strength to produce motor paralysis has resulted in a constant hyperthermia.

3. The minimum concentration necessary to produce paralysis produces a maximum hyperthermia.

4. Recovery of motor function occurs in practically all cases, even though concentrated solutions are used.

5. The procedure is worthy of clinical trial.

A REVIEW OF UROLOGIC SURGERY

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KIDNEY

Innervation of the Kidney.—Serés [1] considers in detail the anatomic and functional significance of renal innervation. He is of the opinion that the renal nerve supply not only influences the kidney by means of its effect on the circulation but also exercises a direct secretory or trophic influence on the kidney. He bases his opinion on work done on dogs by himself and Bellido, in removing the nerves from the renal pedicle. During the first days after the operation the degenerated kidney secretes more urine than the untreated fellow kidney. Likewise after the injection of solutions of sodium chlorid or sugar intravenously, diuresis begins earlier in the treated kidney and lasts longer. This polyuria lasts from eight to ten days. After a month the treated kidney shows degenerative changes. When the operation was performed only on one side the treated kidney showed only slight changes, but when both kidneys were denervated, signs of renal insufficiency appeared in a few days, and death from uremia followed. Serés believes the operation is indicated in man when otherwise decapsulation, nephrostomy or even nephrectomy might be indicated; for instance, in slight hydronephrosis; when only one kidney remains in high grade hydronephrosis; in floating kidney when decapsulation and fixation do not relieve pain; in nephritis dolorosa, and in nephritis hematurica. In the light of the results of animal experimentation one should wait a considerable time after the first operation before denervating the opposite kidney. The technic of the operation is described. An ample lumbar incision, exposure of the kidney, absolute separation of the renal fat, and isolation of the renal

1. Serés, Manuel: Enervation der Niere, Rev. méd. de Barcelona **1**:220-232, 1924; abstr., Ztschr. f. urol. Chir. **17**: 54-56, 1925.

pedicle, so that its elements are completely exposed to view, are the preliminary procedures carried out. The anterior pedicular nerves are extirpated after they have been isolated with a concave sound or with a Kocher sound so that they can be completely stripped from the arteries; the nerves are separated from the veins with a separator 15 mm. wide, and then divided. The posterior pedicular nerves are similarly exposed and divided. Legueu recommends leaving a few of the fibers intact. Fixation of the kidney with partial decapsulation, drainage and suture complete the operation. Serés has performed the operation seven times for nephritis dolorosa and movable kidney with slight pelvic dilatation and pain, which simulated that due to stone. In all of these there was relief from pain and polyuria such as was noted in the animal experiments. In one case of nephritis dolorosa only temporary relief was obtained. After a time severe anemia ensued, there was marked diminution in the number of erythrocytes and evidence of renal insufficiency. The patient finally died in prostration. At necropsy the denervated kidney was found to be anemic and to contain a blood cyst in the upper pole. In consequence of this case the author has given up the operation but he is of the opinion that if further studies show which nerves may be sacrificed and which should be preserved the operation may be used again with great benefit.

Nephritis.—Rosenthal [2] considers the theories and clinical results of operative treatment of the so-called medical nephropathies, correlating scientific advances with clinical experience. The assumption of Edebohls that through decapsulation a collateral circulation is established and that the arterial hyperemia thus produced leads to healing of the nephritis is erroneous. Rosenthal considers that the effect of decapsulation is a mechanical one, the pressure brought about by the swelling of the renal parenchyma being released and new channels of lymph drainage being established. A reflex relaxation of the vagus tone is to be considered as possibly at work, this bringing about a bilateral diuresis, even with one-sided operations, a fall in blood pressure, and relaxation of the vessels. Healing of the nephritis and prevention of its progress are not accomplished. This method can be applied clinically only in acute or chronic inflammations associated with anuria. The effects of decapsulation and of nephrotomy are similar, the dangers of after bleeding and of secondary contraction associated with these operations about balancing one another. Rosenthal recommends the one sided operation. He treats most cases of anuria by the less radical measure of venipuncture, edema puncture and, in cases of eclampsia, lumbar puncture. In

2. Rosenthal, Otto: Die Chirurgie der Nephritis, Ztschr. f. Urol. **18**: 70-95, 1925; abstr., Ztschr. f. urol. Chir. **16**: 210, 1924.

progressive cases of contracted kidney, decapsulation is no longer employed. Of the nephropathies not associated with anuria, the comparatively rare true nephrosis may become surgical, when all internal medication fails. In the remaining tubular nephritides, such as that caused by corrosive sublimate poisoning, decapsulation is not employed. In subacute cases the results are uncertain but one should try the operation in eclampsia because of the lack of danger of the procedure and the possibility of success. Very good results have been obtained in treating the pain and colic of patients with nephritis. Here belong the cases of granular atrophy, gouty diathesis and circumscribed nodose inflammation. By separation of the nerves of the capsule the patient is often freed of pain for the period of a year. The effect of decapsulation on massive bleeding is pointed out. The mechanism is not completely understood but the operation does not seem to prevent some residual bleeding.

[ED. NOTE.—The general recommendations of Rosenthal correspond fairly well with those of Rovsing reported some months ago. Undoubtedly the indication par excellence for decapsulation operations is acute renal suppression that will not respond to medical treatment. This, when due to acute nephritis, may in a certain small percentage of cases result in diuresis. However, the trend of opinion is more and more against decapsulation. The employment of decapsulation and stripping of the renal nerves in obscure renal and ureteral colic is discussed at length in the German literature of today. Recently, accurate anatomic descriptions of the renal nerve supply have been presented and efforts are being made to devise methods of resecting the renal plexus from the capsule and the larger vessels in an attempt to cut the afferent pain fibers. Just where this will lead in the field of applied urology is problematic, the clinical reports to date not being conclusive.]

Renal Anomalies.—Löffler [3] reports two cases of horseshoe kidney, both diagnosed at operation. One was complicated by infected hydronephrosis and the other by tuberculosis. Heminephrectomy was done with recovery in each case. The author comments on the difficulty of the preoperative diagnosis of the condition. The incidence of horseshoe kidney in renal operations runs from one in 112 to one in 148, according to statistical reports from long series of cases. Heminephrectomy is the procedure of choice in complicated cases when one-half the kidney and its pelvis is normal. The various steps in the operative technic are mentioned. Preliminary ligation of the vessels to the diseased portion, if these can be isolated, lowers the amount of bleeding

3. Löffler, Leopold: Zur Kasuistik der Hufeisennierenoperationen, Ztschr. f. urol. Chir. **16**: 181-186, 1924.

incident to the resection. The use of the wedge shaped resection of Albarran and the application of the angiotribe of Rovsing are considered unnecessary in the majority of cases. Suture or ligature of the bridge between the two halves of the kidney is necessary, the sutures being tied not too tightly for fear of cutting into the renal parenchyma and establishing a urinary fistula or causing secondary bleeding.

[Ed. Note.—The incidence of infectious diseases in one portion of horseshoe kidneys is well recognized. The morbidity of horseshoe kidney is clearly shown in the relation between its occurrence and the frequency with which it requires surgical intervention. In a compiled series of 68,000 necropsies Carlier and Gerard found eighty horseshoe kidneys, an incidence of one in 850. In a recently published series of 2,424 operations on the kidneys for various conditions, seventeen were on horseshoe kidneys, one in 142. It has been suggested that the best exposure in operation on a fused kidney may be obtained by the anterior transperitoneal incision (Rovsing). This is advantageous, because it reveals the portion of the kidney most difficult to deal with, that is, the isthmus. However, there are some objections to this exposure. Since the kidney is often more or less infected, this method exposes the peritoneum to infection. This is not always a serious matter and can often be satisfactorily controlled; however, in some cases it may amount to a grave disadvantage. It would be difficult to expose a horseshoe kidney satisfactorily through a posterior incision; but if this type of incision is converted into a posterolateral incision, the exposure and working field will be just as adequate as with an anterior incision. If necessary, the anterior limb of the posterolateral incision can be carried farther forward than usual, and in this way the isthmus can be exposed to view without the peritoneum being opened. When heminephrectomy is performed for infection, multiple stones or functionless kidney, it may at times be best to perform a subcapsular operation, and tie or suture over the capsule of the isthmus. Unless there is some special reason, it is best to remove the capsule and kidney together. This, of course, is always the rule in the presence of tuberculosis and neoplasms. The method of dealing with the cut off end of the isthmus will depend on the accessibility and the amount of infection. If possible, the stump should be sutured over to control oozing, and then covered, by bringing the capsule over. If the patient is very large and there is considerable infection, and the isthmus is well controlled by a clamp, it is best to leave the clamp in place for several days. It acts as a good drain, and will care for the isthmus very well. During the first few days, the clamp will possibly cause some pain; but otherwise, in our experience, it has made no difference whether we sutured the isthmus or controlled it by clamp.]

Eisendrath and Phifer [4] reviewed fifty-five cases of double kidney in which total nephrectomy was performed. Fifteen cases of primary heminephrectomy have been reported by various authors. Legueu has reported a case in which total nephrectomy was performed on one side and heminephrectomy on the other side for tuberculosis. Eisendrath has reported a case in which so far as can be ascertained, bilateral heminephrectomy was performed for the first time. Bilateral infected hydronephrosis was present in the lower portions of the double kidneys with stone formation on the left side. The diagnosis was made by cystoscopic examination. An interval of two months was allowed between the operations. In each instance a single blood supply was found for the two parts of the kidney.

Perrier [5] reported the case of a woman, aged 50, who had been subjected to painful crises in her left side since her pregnancy thirty-two years before. The crises had been more frequent in recent years and were accompanied by cloudy urine and fever. The roentgenologic examination was negative. The left ureteral catheter entered only a few millimeters and no urine was obtained; normal urine was obtained from the right kidney. The left kidney being functionless, an incision was made in the left lumbar region but no kidney was found; an exploring hand pushed downward through the inferior part of the incision encountered a soft pelvic mass, applied against the sacrum. Nothing more was done at the time. Two weeks later this mass, which was a pyonephrotic sac of a pelvic kidney, was removed through an abdominal incision; the sac was 30 cm. in diameter, and was applied against the concavity of the sacrum and filled with purulent material. The sigmoid and mesosigmoid were utilized to separate the pelvis from the abdominal cavity, and drainage was established through the vagina. The kidney had been reduced to a thin pouch, smooth on its inner aspect and covered with fat outside.

[Ed. Note.—In this case the kidney had been destroyed by compression of the pregnant uterus. The ureter is generally short, rigid, fixed and tortuous, entering the bladder at the normal site; it frequently becomes kinked or obstructed; dilatation of the pelvis occurs quite frequently in these misplaced kidneys. A pelvic kidney is covered with peritoneum. When it is low in the pelvis the uterus and rectum may be pushed to one side. In an occasional case, in women, they are covered by the broad ligament and ovary, or these structures may be entirely missing. They are usually normal but vary in size; and may be large and comprise the bulk of the renal tissue present. When this occurs the

4. Eisendrath, D. N., and Phifer, F. M.: Bilateral Heminephrectomy in Bilateral Double Kidney, J. Urol. **13**: 525-535 (May) 1925.

5. Perrier, C.: Pyonephrose d'un rein en ectopic pevienne, J. d'urol. **19**:29-32, 1925.

kidneys are usually flat and irregular or mushroom in shape, and are situated either over the iliac vessels or low in the pelvis. Pelvic kidneys are lobulated, distorted, as in the case above, by neighboring organs and muscles, and often rounded and furrowed by vessels. Not infrequently fetal lobulation persists, and may also be present in the opposite kidney. The vessels commonly arise from the lower part of the aorta or from the iliacs. In most cases branches arise from several vessels as there is no regional artery of sufficient size to supply a branch the size of the renal. The multiple vascular supply is probably due to the persistence of fetal vessels which supplied the kidney as it passed upward and normally atrophied. Owing to incomplete rotation of the kidney, the renal pelvis generally faces anteriorly; it is small and usually well protected by surrounding parenchymal tissue. It is necessary to establish the presence of a functioning kidney before operation because the pelvic kidney is frequently a solitary one.]

Renal Stone.—A study of the comparative value of different operatons for renal lithiasis made by Rafin [6] is based on his personal results and on the reports from Cifuentes (Madrid), Brongerema (Amsterdam), and Tardo (Palermo). The cases are classified as simple and complicated, the latter being characterized by the following conditions: bilaterality of the lithiasis, coexistence of renal and ureteral calculus, coexistence of cancer or tuberculosis and lithiasis. In the following statistics he deals only with the simple cases.

After pyelotomy there were no deaths in thirty-six operations in Rafin's [6] series; after nephrotomy death occurred in 11 per cent. of forty-two aseptic cases and 9.5 per cent. of septic cases. The combined statistics from the four authors showed a mortality of 2.4 per cent. after pyelotomy in 1,401 cases; after nephrotomy the mortality was 8.15 per cent. in 1,084 aspectic cases, and 13.4 per cent. in 992 septic cases. After nephrectomy 6.6 per cent. of Rafin's thirty-two patients and 8.4 per cent. of 1,873 patients of all four authors died.

The postoperative complications were hemorrhage after pyelotomy (one case in which secondary nephrectomy was necessary), and hemorrhage after nephrotomy (two deaths from hemorrhage, one case being followed by secondary nephrectomy). Cifuentes in 616 cases of nephrotomy reported serious hemorrhages in eighty-five, in thirty-six of which secondary nephrectomy was necessary; twenty-two of the patients died.

In Rafin's [6] series, lithiasis recurred after pyelotomy in 23 per cent. of cases, after nephrotomy in 15 per cent., and after primary nephrectomy in 3.3 per cent. In the combined series lithiasis recurred after

6. Rafin: Valeur comparée des diverses interventions pour lithias rénale, XXIV session annuelle de l'association française d'urologie, J. d'urol. **18**:523-524, 1924.

pyelotomy in from 0 to 25 per cent. of cases (aseptic) and in from 7 to 50 per cent. of cases (septic); after nephrotomy in from 3.2 to 17 per cent. of cases (aseptic), and in from 7 to 54 per cent. of cases (septic); after nephrectomy in from 1 to 4 per cent. of cases.

Clearing of infected urine is unusual after nephrotomy.

The conclusion is that for aseptic calculi, pyelotomy remains the method of choice whenever it can be performed, whereas in infected lithiasis most surgeons usually prefer nephrectomy.

At a meeting of the Societé de Chirurgie de Lyon, Rochet [7] suggested dividing cases of bilateral renal calculus into three categories in order to facilitate the selection of surgical procedures. In cases in which there are small stones in both kidneys, prolonged medical treatment is often enough to bring about a cure of long duration. Indications for surgical intervention are repeated and prolonged colic with hematuria (operation on the responsible kidney) and migration of an irregular calculus which may encroach on the ureteral wall. In cases in which there are small stones in one kidney and large ones in the other, operation is indicated. Some surgeons attack the more diseased kidney, arguing that the healthier one holds good and is not exposed to the possible eventual necessity for nephrectomy on account of operative accidents. Rochet prefers to perform either pyelotomy, if possible, otherwise nephrotomy, on the best kidney, because this one, if not operated on first, may be seriously obstructed by a stone. In cases in which there are large stones in both kidneys, conservative procedures are indicated because these cases are usually associated with what the author calls a "catarrhe lithogen," an inflammatory condition predisposing to the formation of stones; and they are usually found in persons of advanced age affected with diabetes or cardiovascular disease. Moreover the patient may still live comfortably for many years without too much trouble.

Goyena [8] emphasizes the value of renal percussion in the diagnosis of renal stones; this was first described by Giordano of Venice. The symptom is not constant, but is frequently present and sometimes definitely marked. If a stone is present the percussion of the dorsolumbar region of the spine, by the cubital border of the hand, causes a violent pain at the level of the affected kidney. Three cases are cited in which he diagnosed lithiasis almost exclusively by this method, although a diagnosis of appendicitis and sciatic pain had been made elsewhere. Diagnosis was each time confirmed operatively. Goyena found the deep percussion test positive and on this basis correctly diagnosed renal stone.

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7. Rochet: Quelques cas de néphrolithiase bilatérale, Lyon chir. **21**: 583, 1924.

8. Goyena, J. R.: De la percussion profonde de la région lombaire dans la lithiase rénale, Presse méd. **33**: 19-20 (Jan. 7) 1925.

Chauffard and Debray [9] note that the coincidence of renal and biliary calculi is not infrequent. Senac found this coincidence ninety-six times in 166 cases of biliary lithiasis; Bouchard thirty-four times in 100 cases and Willemin 149 times in 251 cases. The two last figures seem to them somewhat above the usual occurrence, but Willemin probably took into consideration simple deposits of urates. Chauffard and Debray, trying to consider the reciprocal relations between these two forms of lithiasis, and looking for a common cause for this double situation of calculi, studied the chemical constitution of blood in more than twenty cases of each of them. They found that, if hypercholesterinemia was the rule in cases of both renal and biliary calculi, there was no hyperuricemia associated with biliary calculi, whereas this hyperuricemia was present in the majority of cases of renal lithiasis. The immediate conclusion formed is that the "gravelle urique" creates a state favorable to the production of aseptic cholelithiasis and acts as a predisposing cause; primary biliary lithiasis remains independent of the hyperuricemic states of which "gravel and gout" are the best defined types. The clinical findings corroborated this conclusion: Chauffard and Debray cite twelve cases of "bilithiasis" as they call this condition, in which renal colic started in eleven well ahead of the biliary colic. Only once had the sequence been reversed. Willemin, in seventy cases of "bilithiasis," had noted the renal colic appearing first forty-five times; at the same time as the biliary colic, five times, and after it, twenty times.

A patient of Cotte's,[10] a woman, aged 40, had been complaining of painful intermittent crises for fourteen years; they had all the characteristics of renal colic and were separated by periods of perfect health. A tumor appeared a few months before her admission, disappeared and reappeared definitely later, after an especially painful crisis. Examination revealed the tumor on the right side. Roentgen rays showed a large stone in the right kidney with several small ones; there also was a fairly large calculus in the left kidney. By ureteral catheterism urine containing 9.85 gm. of urea for each liter was collected from the left side, but nothing came from the right side, which was apparently obstructed in the upper ureter. It was decided to remove the right kidney, which was hydronephrotic and measured 28 by 17.5 cm. From a therapeutic standpoint, Cotte preferred to leave the healthy kidney quiet and not try to improve its function by removing the stone, but removed the completely obstructed hydronephrotic kidney, which was useless and painful. From an anatomic and etiologic point of view, the

9. Chauffard, A., and Debray, M.: Rapports réciproques des lithiases du rein et de la vesicule biliaire, Presse méd. **33**:129-130 (Jan. 31) 1925.

10. Cotte, G.: Hydronéphrose et lithase rénale bilatérale, Lyon chir. **21**: 762-763, 1924.

question arises whether this was a calculous hydronephrosis or a congenital hydronephrosis with secondary lithiasis. In this case the ureter itself contained no calculi; these were in the renal parenchyma. It seems more logical to admit a secondary lithiasis due to a malformed kidney and hydronephrosis. The stone shown by the roentgen ray on the other side would be no objection to this hypothesis. That kidney, too, might be similarly malformed.

Richter [11] reports a case of a man who complained of symptoms typical of renal calculus for six or eight years. The roentgen ray revealed an irregularly shaped calculus of the coral type occupying three of the calices in the lower pole of the left kidney. The preoperative diagnosis was renal calculus associated with some pyonephrosis on the affected side. At operation the left kidney was well exposed through a lumbar incision. The lower third of the kidney was found to be replaced by a thin walled sac containing turbid urine and several calculi. The renal tissue was so completely destroyed that its removal seemed advisable. The remaining two thirds of the kidney was firm and grossly normal in appearance. In order to conserve this normally functioning portion of the kidney and at the same time to remove the diseased tissues, partial resection was decided on. A wedge shaped section including the entire sacculated lower third, extending down to the pelvis and going well back into firm normal tissue, was excised. The cut margins were accurately brought together with catgut and the pelvis was sutured. Hemorrhage was prevented by digital pressure on the renal vessels maintained by an assistant. Three months later the patient felt perfectly well.

Renal Tumors.—Cabot [12] divides the malignant tumors of the kidney into three main groups: (1) the so-called Grawitz tumor; (2) the tumors of early childhood, and (3) the tumors of the renal pelvis. The first group are usually found in adult life, are generally slow growing, and have a tendency to metastasize. The renal tumors of childhood usually remain localized throughout their course. Like other tumors of childhood they grow rapidly and are highly malignant. Tumors of the renal pelvis are similar to tumors of the urinary bladder. They vary in their degree of malignancy and have a marked tendency toward implantation along the course of the ureter. The mortality following the removal of Grawitz tumors has always been comparatively high. If a lower mortality rate is to be achieved, it will be as the result of methods which preclude serious loss of blood and avoid entire invasion of

11. Richter, H. M., and Zimmerman, L. M.: Resection of Kidney for Calculous Pyonephrosis, Surg., Gynec. & Obst. **40**: 810 (June) 1925.

12. Cabot, Hugh: Malignant Disease of the Kidney, South. M. J. **18**: 99-103 (Feb.) 1925.

the tumor itself. This can be accomplished only by obtaining free access to the tumor, to the end that the main blood supply may be relatively easy of access and also to the end that the whole tumor, including the fat capsule and even the suprarenal gland, may be removed without invading the privacy of the new growth. It is apparently true that this tumor is most commonly attacked through the classical loin incision which is so eminently suited to dealing with most of the pathologic conditions of the kidney. It does not, however, give easy access to the kidney and in many cases the danger of getting into a line of cleavage between the fat capsule and the tumor is not easily avoided.

Cabot has entirely abandoned the loin incision for these cases, as being not well suited to the particular problem, and has adopted a transverse incision which is made at such a level as just to pass the lower border of the lowest rib wherever it may be. This incision is carried from a point well back on the side to the median line of the abdomen. It has the great advantage of doing less damage to the nerve supply than any other incision except the loin incision and for this reason is clearly preferable to any vertical incision planned to attack the tumor through the peritoneal cavity. In Cabot's experience it has commonly been desirable to meet this transverse incision with a vertical incision, which generally extends upward from a point just above the umbilicus well toward the ensiform. This incision in no way interferes with the muscular integrity of the abdominal wall and gives an unexcelled exposure of the tumor. Of course it widely opens the peritoneal cavity and enables the surgeon, under direct sight, to push inward the peritoneum, remove the mesentery of the colon from the surface of the tumor and deal in a bloodless way with the communicating vessels which, though rarely large, are sufficient to besmear the field and lead to trouble. When the peritoneum and the colon have been entirely freed from the surface of the growth it is then possible to deal with it in such a way that the loss of blood is reduced to a minimum. It should be remembered that the line of separation to be sought in these cases is between the fat capsule of the kidney and the retroperitoneal connective tissue. Not only is this the least vascular and therefore most desirable line of cleavage, but by it invasion of the tumor with its bloody consequences is avoided. As there is a definite tendency of this tumor to protrude into the renal vein, unusual care should be exercised in isolating this structure, so that the division of a portion of the tumor which protudes into the vein, leaving it in the pedicle, will be avoided if possible. In the papillary tumors of the renal pelvis it is essential that the entire length of the ureter be removed; the loin incision prolonged to any necessary extent is the best method of approach.

Kretschmer [13] reports a series of fifty-four cases of tumor of the kidney. Forty cases were in males and fourteen in females. The tumor was definitely known to have occurred on the left side in twenty-seven and on the right in twenty-three cases. Pain is a common symptom; it occurred in 77 per cent. of Kretschmer's cases. In thirty-two cases (59 per cent.) a palpable tumor was present. When a palpable growth is present the diagnosis is easy but the patient's chances for cure are not good. Hematuria is the most important symptom. Blood was found in the urine, or there was a history that the patient passed bloody urine in forty-one cases (74 per cent.). All three cardinal symptoms, pain, tumor and hematuria, were present in one third of the cases. Only eleven of fifty-four patients had fever; when fever was present it was usually not marked and in some cases could be accounted for by other conditions. Blood pressure readings were taken in thirty cases. In ten cases the systolic blood pressure was more than 150; in seven of these there was definite evidence of nephritis. Bacteriologic examinations were made in thirty-four cases; in twenty-two cases the urine was sterile. In eight cases the urine from both kidneys was sterile, but culture of the bladder urine was positive; in three cases the urine from one kidney was sterile, but culture of the bladder urine was positive; in one case the cultures from both kidneys and bladder were positive.

Grauhan [14] reviews the progress in urologic diagnosis of renal tumor since the introduction of pyelography and pneumoperitoneal roentgenography in the study of this condition. When the tumor is not palpable, and when pain and hematuria are absent, the exact determination of the condition may rest with the proper application of one of these procedures, especially the pyelogram. Four groups of cases are considered.

In the first group the renal tumor is definitely determinable from the contour of the pyelogram. In the cases of this group the kidney and ureter were somewhat displaced and there was a definite filling defect of the pelvis with obliteration or distortion of one or more of the calices. The pelvis is frequently dilated. The displacement of the kidney is more often toward the median line.

In the second group of cases the tumor can usually be diagnosed from the pyelogram. In a case cited, the ureteral course was found close to the spine and the normal form of the pelvis wae entirely lost, so that incomplete filling with the pyelographic medium was suspected. Pneumoperitoneal roentgenography was used and a second pyelogram was made which proved to be similar to the first. At operation a renal

13. Kretschmer, H. L.: Early Diagnosis of Malignant Disease of the Kidney, South. M. J. **18**: 92-99 (Feb.) 1925.

14. Grauhan: Die Tumorniere im Röntgenbild, Ztschr. f. urol. Chir. **17**: 1-26, 1925.

tumor almost filling the renal pelvis and preventing the filling of the calices by the pyelographic medium was found.

The third group consists of cases in which the pyelogram is almost normal. In one case mentioned the pyelogram showed the kidney and the ureter in normal position, but the upper calices were poorly filled, and a diverticulum-like process was observed lateral to the ureter at the lower part of the pelvis. Other clinical findings suggested a tumor. At exploration a benign tumor of the upper pole, 2.5 cm. in diameter, was found. The diverticulum consisted of an abscess communicating with the ureter.

In the fourth group the renal tumor presents the pyelographic picture of a uronephrosis. This constitutes a large group and may be confusing, as the tumor segments, by interfering with renal drainage, may produce an extensive hydronephrosis or pyonephrosis. Tumor developing in a hydronephrotic kidney also is encountered. Clinically, the indication in either case is nephrectomy so that preoperative differentiation is not always essential. It is noted that papillary tumors are prone to give rise to hydronephrosis. The authors emphasize the importance of pneumoperitoneum in renal roentgenography in depicting changes in the size and contour of the kidney which may be significant.

[Ed. Note.—The diagnosis of renal tumor has been greatly simplified in the majority of cases since the introduction of exact cystoscopic methods, of which the outstanding procedure is the use of the pyelogram. While, as Grauhan points out, the diagnosis may not always be established with certainty, a combination of the urinary findings, the differential function and abnormalities in the pyelogram will often link up with the clinical signs and symptoms. Here and there we find reports of the diagnosis even of papillary tumors of the renal pelvis by such methods.]

Kaufmann and Cashin [15] review the literature dealing with the interrelationship between the suprarenal and the thyroid, and report the case of a woman, aged 68, who gave a history of hematuria, backache and weakness. An adenoma of the thyroid was noted. No cystoscopic examination was made. The patient was given hydrotherapy and dismissed. Three months later she was again admitted to the hospital with hematuria, and cystoscopic examination revealed hypertension and essential hematuria. On a third admission to the hospital she complained of hematuria, weakness, palpitation, nervousness and anorexia. The goiter was the same as before. Tachycardia was noted (120-130). The basal metabolism estimation was + 53.3 per cent. She left the hospital on

15. Kaufmann, J., and Cashin, M. F.: A Case of Hypernephroma Associated with Thyroid Activity, Canad. M. A. J. **15**:37-40 (Jan.) 1925.

iodin treatment, returning in a month to the urologic service on account of hematuria. The toxic goiter signs were more marked and the right kidney was palpable. Nephrectomy was performed. Pathologically the renal tumor was a hypernephroma involving the upper pole of the right kidney. The patient subsequently died.

The case is reported to show the interrelationship between the hypernephroma and the toxic goiter, illustrating a relationship between the suprarenal and the thyroid.

Renal Cysts.—Blanc [16] reports two cases of unilocular cyst of the kidney. The first was that of a man, aged 57, who had been suffering with intermittent shooting pains in the right renal region for ten years; a mass 10 cm. in diameter had gradually appeared during the last six months. It was fluctuant, circumscribed, not tender, smooth, and not adherent to the abdominal wall. He also had occasional attacks of hematuria, pyuria and frequency, and short periods of fever. Tests revealed moderate bilateral diminution of renal function. Pyelograms revealed bilateral dilatation of the pelvis and a vertebral convexity of the ureter on the affected side. At operation, a unilocular serous cyst was found at the lower pole of the right kidney together with a smaller cyst. The cyst was emptied and resected; the wound was drained, and the patient recovered completely. The second patient, a woman, aged 51, had a similar abdominal mass which had increased gradually to about 20 cm. in diameter and occupied a suprapubic position. There had been no pain, no dysuria, no hematuria and no fever, and the urine was clear. The renal function was similar on both sides. The cystoscopic examination and pyelogram were negative. A single cyst of the kidney was found at operation; it was punctured and resected, but owing to the accidental severance of an abnormal artery having caused a persistent hemorrhage, nephrectomy was performed; uneventful recovery ensued. Blanc mentions that the most important question arising in cases of this type is the diagnosis; one must determine whether a renal tumor is present, whether the mass is cystic and whether it empties by ureteral catheterization. The volume and consistency of the mass in the first case and the general symptoms were not in favor of a tuberculous infection, but infected hydronephrosis was difficult to discard without taking into consideration some complementary tests. Against this diagnosis were the following facts: the pyelogram showed that the kidney was in a normal position; ureteral catheterization showed that there was no retention in the pelvis; the capacity of the pelvis was 24 c.c. as determined by injection of fluid and recovery of it from the renal pelvis. Renal function is not usually lowered in cases of single cyst of the kid-

16. Blanc, H.: Deux cas de kystes du rein, J. d'urol. **19**:5-12 (Jan.) 1925.

ney. Hematuria is exceptional in such cases though Brin found it in five of fifty-five cases. Treatment of large cysts of the kidney consists of resection of the sac, partial nephrectomy or, in rare cases, nephrectomy.

Renal Tuberculosis.—Medlar and Sasano [17] state that even when genital tuberculosis is ruled out by an apparently normal condition of the kidney, bacilli of tuberculosis occasionally are found in ureteral urine. The hemic route is the most common one in tuberculous infection of the kidney; infection through the lymphatics or ureters is rare. Four rabbits and twelve guinea-pigs were inoculated intravenously with bacilli of tuberculosis. The urine was examined for bacilli and later the kidneys from these animals were serially sectioned; in all over 30,000 sections were examined. No evidence to support the belief that bacilli of tuberculosis are excreted by a normal kidney was found. All infections were by way of the blood. Usually there were multiple foci. Evidence of the healing of individual tuberculous lesions of the kidney was found. Such a condition is probably rare, although more common than now believed. Medlar and Sasano state that negative findings do not rule out tuberculosis and that the size of the tuberculous lesion is no criterion of the number of bacilli present.

Bernadet [18] gives a detailed observation of a case of renal tuberculosis in a girl, aged 20 years. There was marked urgency and dysuria without other symptoms. Her condition was improved by instillation of silver nitrate solution and the administration of methenamine, but six months after the onset, frequency, dysuria, pyuria and vesical tenesmus still persisted. A little pus but no bacilli were found in the urine; there was no blood and no history of hematuria. After ten irrigations with silver nitrate, varying in concentration from 1:3,000 to 1:1,000, a notable improvement took place; cystoscopic examination revealed a few ulcerations in the dome of the bladder. Subsequent catheterization of the ureters showed the presence of bacilli of tuberculosis in the urine from the left kidney. Nephrectomy was performed and a complete cure resulted. The kidney exhibited typical tuberculous lesions at all stages.

Thévenot,[19] studying the bladder after nephrectomy for renal tuberculosis, states that all lesions may completely disappear or the tuberculous lesions alone may subside, leaving only areas of congestion and yellow patches, or that finally the specific lesions may persist. The ureter usually closes slowly, the obliteration being due to the diminution

17. Medlar, E. M., and Sasano, K. T.: Experimental Renal Tuberculosis with Special Reference to Excretory Bacilluria, Am. Rev. Tuberc. **10**: 370-391, 1924.

18. Bernadet, G.: Un cas particulier de tuberculose rénale, J. d'urol. **19**:132-134 (Feb.) 1925.

19. Thévenot: La Vessie des néphrectomisés pour tuberculose rénale, J. d'urol. **18**: 410-414, 1924.

of the infection, which brings about the gradual welding of the walls. Rarely does the ureter continue to suppurate. From a clinical standpoint, before the nephrectomy, one notes frequency, pain during and after micturition, pyuria and hematuria with diminution of the bladder capacity. After nephrectomy, the patients may be grouped into three categories: (1) those in whom all symptoms disappear; (2) those who present a momentary improvement soon followed by an aggravation of lesions in the opposite kidney or in the genital organs, and (3) patients who continue to have various urinary disturbances. Some of them have clear, nontuberculous urine, but the frequency continues; others have frequency, pain and pyuria due to other infections; others still harbor the bacilli of tuberculosis in the urine. From an etiologic standpoint the untoward results may be divided into three groups: (1) cases in which the persistence of disturbance of the bladder is due to abnormal sensitiveness of the neck of the bladder, often to retraction or sclerosis of the vesical muscle; (2) cases in which that persistence is due to a cystitis caused by added infection, and (3) cases which can be explained by the invasion of the opposite kidney, the development of genital tuberculosis or continued suppuration of the remaining ureteral stump, as in some cases in which vesical lesions continue to develop primarily. The prognosis is favorable for the first and the second group and fairly favorable for the third group if the lesions remain localized to ureter and bladder.

Thévenot reviews the surgical procedures that may deal with the diseased ureter, with the bladder, or with its nerves. Primary ureterectomy has been abandoned in France, as often it is either useless or aggravates the postoperative condition. Some surgeons during the operation unite the ureter to the skin; others try to destroy the ureteral mucosa by cauterization with acid injections. In some cases secondary nephrectomy has been carried out. Operations on the bladder and its nerves comprise curettage of the bladder through the urethra or after cystostomy, dilatation of ureter and neck, sphincterotomy and section of the vesical nerves. Exclusion of the bladder may be secured by cystostomy, total cystectomy, uretero-entero-anastomosis, iliac or lumbar ureterostomy or nephrostomy of the remaining kidney. Discussing these different methods, the author expresses the opinion that prolonged medical treatment often leads to cure. Operation should be exceptionally resorted to and preference should be given to sphincterotomy and operations on nerves or exclusion of the bladder by ureterostomy or nephrostomy. The author insists especially on the necessity of practicing nephrectomy for tuberculosis as early as possible, because the earlier the vesical lesions, the more satisfactory the end-result.

Reschke [20] reports twenty-three cases of a ruptured hydronephrotic sac besides two of his own. One case was that of a girl, aged 5 years, who fell on the left side of the abdomen. Immediately afterward marked tenderness and rigidity appeared. The right renal region was tender. Bloody urine was passed. The temperature and pulse were high. Renal exploration was carried out on account of the suspicion of renal injury. The kidney was a ruptured sac 10 cm. in diameter and was extirpated. The second case reported was that of a man, aged 21, who was kicked by a horse in the upper part of the left side of the abdomen. Urinary suppression followed and he came to the clinic in a much exsanguinated condition. There was marked rigidity on the left side. Catheterization yielded almost pure blood. At operation a large ruptured left sided hydronephrosis was found. Nephrectomy was performed. The symptoms of this condition include prostration, tenderness and rigidity in the renal area, pressure and tumor in the flank, ballottement, meteorism, vomiting, belching, anuria, hematuria, and increase in the pulse and in the temperature. To these the author adds the fact that the pallor of the skin and mucosa is great and the lividity and coldness of the extremities is striking. The diagnosis of a ruptured hydronephrotic kidney is seldom made before operation. In fact it is made only when it is already known that the patient has hydronephrosis. Expectant treatment is not indicated. The only contraindication to nephrectomy is the possibility of renal insufficiency on the other side. Nephrotomy is advised against because the danger of infection of the large ruptured sac is extreme, death having occurred in three or four cases when this was attempted. Quick surgical intervention, with nephrectomy as the procedure of choice, is the recommendation of the author.

[ED. NOTE.—It is remarkable that more cases of rupture of a hydronephrotic sac are not encountered as the thinning of the renal parenchyma and pelvis incident to the process might be thought to predispose to the condition. Probably the slow development of hydronephrosis in most cases allows for fibrosis in the pararenal tissues which stabilizes the renopelvic wall in such a way as to prevent rupture. At any rate the condition is seldom encountered clinically. The differentiation from the acute infected type would seem to be made chiefly on the basis of gross hematuria and the marked prostration, features which Reschke emphasizes.]

Aneurysm of the Renal Artery.—Schramm [21] reports a case of aneurysm of the renal artery caused by a knife wound. One and one-half years after injury the kidney and aneurysmal sac were removed.

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20. Reschke, Karl: Über Hydronephrosenrupturen, Deutsch. Ztschr. f. Chir. **185**: 137-142, 1924.

21. Schramm, Hilaire: Aneurysm of the Renal Artery, Ann. Surg. **81**: 105-107 (Jan.) 1925.

The sac and the kidney were adherent and the sac adhered so closely to the wall of the aorta that it was impossible to separate them without rupturing one or the other. Therefore, two curved clamps were laid on the neck of the sac 1.5 cm. externally from the wall of the aorta, and the sac and the kidney were cut away. A thin but strong stream of blood gushed between the clamps, the ends of which did not meet exactly, but the hemorrhage was easily stopped by a third clamp. The walls of the sac were now sewed together along the clamps with a mattress suture and the clamps were removed; there was no further bleeding. A second row of stitches was added nearer the aorta and the suture line covered with adjoining connective tissue by a modified Lembert suture. A rubber tube was introduced to the bottom of the wound. The removed tumor was a sac of about 8 cm. in diameter, filled loosely with fresh, partly with older, clots; its walls were thin, and on microscopic examination well developed elastic, but no muscular fibers were found. The kidney lay on the external wall of the sac; in its upper end there was a hole 2.5 cm. in diameter, communicating with the renal pelvis.

Thirty-four cases of renal aneurysm were found in the literature. Sixteen of them were cases of true spontaneous aneurysm following sclerosis or fatty degeneration of the walls of the artery. The average age of the patients was 56. In eighteen cases of traumatic aneurysm the age of the patient had no influence; the trauma was fifteen times subcutaneous; only three times was there an open wound of the kidney. The signs of renal aneurysm are not sufficiently characteristic, and the diagnosis was certain in only six cases before operation. Death may occur soon after the appearance of the first symptom although usually the attacks of pain and hematuria last some days, then disappear for a variable time, later returning with greater severity, exhausting the vital forces of the patient and causing death several months later. All the patients treated conservatively died; of nine patients operated on, two died, the remainder were cured. The operation is almost always serious and has to overcome many difficulties; the separation of the aneurysm from the kidney in most cases was impossible. The bursting of the sac caused a mortal hemorrhage in a case reported by Morris, and a patient of Skillern could be saved only by clamping the torn wall of the sac and leaving the clamps in the wound; they were taken off on the fifth day and the hemorrhage did not return. In one case it was possible, after the sac was opened, to find the hole in the renal artery and close it with a suture; the kidney was left in situ, and its function was normal. Because of this danger of hemorrhage in difficult cases it has been advised that the peritoneal cavity be opened, the renal artery separated, this vessel ligated at its origin from the aorta and the extirpation of the aneurysmal sac and kidney then completed.

Perirenal Bleeding.—Rosenburg [22] differentiates subcapsular perirenal hematoma into several types: (1) those cases which arise through erosion of blood vessels from tuberculosis or tumor; (2) cases associated with hemophilia, and (3) cases associated with inflammatory processes in the renal parenchyma. Again we may differentiate those cases in which the bleeding is between the kidney and the capsula fibrosa and those in which the bleeding is of the true capsule, causing true extracapsular perirenal hematoma. It is with the latter that Rosenburg particularly deals. The etiology of massive extracapsular bleeding is not clear. Cases associated with aneurysm of the ovarian artery and with aneurysm of the abdominal aorta are mentioned. Further cases are cited in which the hemorrhage is associated with nephritis, contracted kidney and other features that imply that sclerosis of the arteries is a cause. The analogy to essential hematuria in such instances is drawn. Perinephritis is found in such cases at times, but whether this is a cause or a result of the hematoma is not clear. Young people seem to be more frequently affected than old. Noteworthy is the fact that in most cases the urinary findings at the outset at least are normal. Rosenberg reports a case in a man, aged 30, who had for fourteen days suffered from pain in the right renal region, had normal urinary and roentgenographic findings and who developed, while under observation, a septic temperature. The pain and tenderness over the right kidney led to puncture and aspiration and the diagnosis of perinephritic abscess. At operation an extracapsular hematoma was found. Decapsulation of the kidney with drainage was performed. Recovery took place. There was a history of minor trauma to the right renal region. The author feels that such cases are in most instances the result of trauma to the perirenal tissues with rupture of the extracapsular vessels. Nearly always on close investigation of the history, injury in some form is to be found. The perinephritis and changes in the cortical portions of the kidney, hematonephrosis, and hydronephrosis when present, are felt to be secondary to the pressure changes of the hematoma, or to the processes associated with the absorption of the blood.

[Ed. Note.—Renal trauma unassociated with rupture of the kidney and with hematuria is certainly possible, and certain minor injuries associated with bleeding which does not reach the pelvis occur from time to time. Minor injuries and soreness in the side which lasts a few days and gives no gross symptoms may be associated with slight bleeding which on absorption and secondary scar formation accounts for some of the unusual pictures of adherent renal capsules seen at necropsy occasionally. Undoubtedly sclerosis, syphilitic vascular disease, and

22. Rosenburg, Albert: Über das sogenannte essentielle extrakapsuläre perirenale Hämatom, Ztschr. f. urol. Chir. **16**:155-164, 1924.

other forms of arteritis are predisposing factors, yet the frequent occurrence of this disease in the young, when these other factors are likely to be absent, argues for trauma, which causes a sort of concussion or bruising of the renal fossa and its contents, with secondary bleeding in consequence, if the injury has been severe enough.]

Baló [23] had the opportunity to observe eight cases of bleeding in the renal region. Of these he investigated two kidneys removed, and in six cases necropsy was performed. The source of the bleeding was the spermatic artery in one case, the abdominal aorta in another, and in the remainder the kidney itself or the vessels of the fatty or fibrous capsule. Clinically the diagnosis of perirenal bleeding may be suspected if there is suddenly appearing pain in the renal region, accompanied by signs of peritoneal irritation and a sudden marked tumefaction in the kidney area. The anatomic basis for perirenal apoplexy rests on the fact that it may arise from the kidney, its fibrous or fatty capsule or vessels of the suprarenals or muscles. For the most part there has been previous disease, such as syphilis, sclerosis and ruptured arteries, which is brought about by traumatic insult of some kind. In young patients hemophilia must be considered as a cause. Perirenal apoplexy may be acute or chronic. According to the site of the bleeding, intracapsular and extracapsular hematomas may be distinguished, especially in the acute stage. In chronic cases, when the hematoma has been changed into a cyst filled with serous fluid, intracapsular and extracapsular hygroma renis may be distinguished. Such hematomas may lead to perirenal or paranephritic abscesses, or resolution, with the formation of a cicatrix.

Hematuria.—Kretschmer [24] has reviewed 933 cases of hematuria. The great majority of cases occurred in patients between 30 and 70 years; 690 were in males. A diagnosis was made in 97 per cent. of available cases. In 331 (39 per cent.) the bleeding was from the kidney. The main conditions according to their prevalence are tuberculosis, stone, pyelitis, malignant tumors and nephritis. In 307 cases (37 per cent.) the bleeding was from the bladder. In 235 (76.5 per cent.) tumor was the inciting cause of vesical hemorrhage; stone ranked second, and tuberculosis third. Lesions of the prostate accounted for 126 of the cases (15 per cent.). In sixty-four cases the hematuria was due to benign hypertrophy and in forty-three to carcinoma. The hemorrhage was due to ureteral lesions in fifty-four cases of which forty-eight were due to stone and five to stricture and to carcinoma. Excluding traumatic cases and acute gonorrheal infection, urethral lesions were

23. Baló, Jozsef: Beiträge zum Krankheitshild der Apoplexia perirenalis, Magy. orv. Arch. **24**: 295-310, 1923; abstr., Ztschr. f. urol. Chir. **16**: 207, 1924.

24. Kretschmer, Herman: Hematuria; a Clinical Study Based on 933 Consecutive Cases, Surg., Gynec. & Obst. **40**: 683-686 (May) 1925.

rarely the cause of bleeding; in only six cases was the bleeding urethral. In all, tumor or new growth was the most frequent cause of bleeding. In 325 of all cases, tumor somewhere in the urinary tract provoked the hemorrhage. If benign hypertrophy of the prostate is regarded as a new growth, sixty-four more cases may be added, and a total of 389 cases will be reached, indicating that in 47 per cent. of all cases hematuria is due to new growths. Stone ranked second as the causative factor of bleeding, being present in 154 cases (18.5 per cent.) and tuberculosis, third, in ninety-seven cases (12 per cent.). Acute infections were present in eighty-nine cases (11 per cent.), and nephritis was the cause in twenty-seven cases (3.2 per cent.). Hematuria is only a symptom, but it should always be considered as indicative of the presence of serious organic disease in the genito-urinary tract. Every case of hematuria should be subjected to complete, comprehensive genito-urinary examination to determine, first, the origin of the blood, and, second, the cause of the bleeding.

The clinical picture of essential hematuria is becoming more and more restricted in a true sense. Tumors, inflammations, tuberculosis, nephritis and small stones are being found more frequently on repeated examination as causes of obscure bleeding. Unilateral bleeding of obscure origin is often attributed to unilateral nephritis. However, a review of the literature shows many cases in which tissue has been removed from the bleeding kidney without much, if any, anatomic evidence of disease. Janssen [25] considers an hysterical element and angioneurotic processes as unlikely causative agents. A case is reported in which the pathologic examination of the removed kidney showed that the smaller arteries possessed larger or smaller defects of the inner and the outer elastic coats without any evidence of inflammatory processes being present. The muscular coats showed here and there slight atrophy. This accounted, according to the opinion of the author, for a diapedesis of blood cells through the vessels. Such a condition of the renal vessels is regarded as a congenital anomaly and it is attempted to explain certain cases of essential hematuria on such a basis.

[ED. NOTE.—From time to time a new pathologic report is brought forward with the idea of explaining just how the kidney bleeds without an obvious gross or microscopic lesion to account for it. The arterial defect noted is worthy of consideration and microscopic investigation of further cases should be carried out with this in mind. Probably some defect in the arterial system is behind essential hematuria or at least some cases of essential hematuria. Whether this is congenital, developmental, or due to infectious processes or to toxic effects on the arterial walls with consequent diapedesis remains to be shown.]

25. Janssen, P.: Zur Frage der Nierenblutungen aus nicht erkennbarer Ursache (essentielle Hämaturie), Ztschr. f. urol. Chir. **16**: 87-95, 1924.

(To be continued)

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